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INDEX

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General Information

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Bird-Headed Dwarfs

Studies in Developmental Anthropology Including Human Proportions

By HELMUT P. G. SECKEL, M.D.

Professor of Pediatrics, The University of Chicago, Ill. USA

VIII + 241 pages, 64 figures, 1960 sFr. 54.– (US $ 13.–)

From the "Introduction":

Regarding method, one purpose of the monograph is description. That is to say, complete documentation, numerical if possible, is attempted of a maximum number of objective features of nanocephalic dwarfism. This, besides in itself being a scientific aim, is also deemed useful in view to future observers who may find completeness of data valuable for such studies as they may wish to undertake beyond the interest and the ken of the present writer. The second purpose of the monograph is analysis of the assembled data. Techniques and methods are outlined in detail; they are those of **clinical pediatrics, endocrinology, metabolism, cytology, teratology, genetics, pathology, roentgenology, anatomy and anthropology, orthodontics, neurology and child psychology** (Chapter III to VI). In the third place, the analyzed data are discussed and commented upon under three different headings, differential diagnosis, etiology and pathogenesis (Chapter VII, VIII).

Table of Contents:

S. KARGER Basel (Switzerland) · New York

Fortschritte der Geburtshilfe und Gynäkologie
Advances in Obstetrics and Gynaecology

Herausgegeben von / edited by A. REIST, Zürich

Vol. 11

Zum Problem der Toxoplasmose
The Problem of Toxoplasmosis

Index

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(«Bibliotheca Gynaecologica» Fasc. 22)

BASEL (Schweiz) S. KARGER NEW YORK

L 46

Acta genet. *11:* 185–195 (1961)

From the State Institute for Blood Group Serology, Statens Rättskemiska Laboratorium, Stockholm, the Department of Bacteriology, Karolinska Institutet, Stockholm, the Institute for Medical Genetics and the Institute of Plant Systematics and Genetics, Uppsala, Sweden.

DISTRIBUTION OF THE GC-SERUM GROUPS IN NORTHERN AND CENTRAL SWEDEN

By JAN HIRSCHFELD and LARS BECKMAN

1. Introduction

Recent developments of new methods for serum protein separation, such as the methods of starch gel electrophoresis and immuno-electrophoresis, have revealed many new serum protein polymorphisms in man. Thus, *Smithies and Walker* (1955) have shown that the haptoglobin variants of human serum detectable by means of starch gel electrophoresis are genetically controlled. *Smithies and Hiller* (1959) have demonstrated that the variable, iron-binding β-globulins in man are controlled by a series of multiple alleles.

By means of immuno-electrophoresis, which is a combination of agar-gel electrophoresis and an immunological reaction in agar medium devised by *Grabar and Williams* (1953), more than 25 immunologically and electrophoretically different components have been demonstrated and defined in normal human sera (*Hirschfeld* 1960 a). With a slightly modified immuno-electrophoretic technique (*Hirschfeld* 1960 b) qualitative variations in the immuno-electrophoretic patterns of normal human sera (*Hirschfeld* 1959 a), monkey sera (*Beckman, Hirschfeld and Söderberg* 1961) and rabbit sera (*Hirschfeld* 1959 b) have been found. In human sera these variations can be attributed to two immunologically and electrophoretically different systems, which, independently of each other, might occur in an electrophoretically fast type (1–1), a slow type (2–2) or both fast and slow type (2–1) in different sera, thus allowing a grouping of normal human sera into any of 9 immuno-electrophoretically different types.

One of these variable serum systems has been identified with the haptoglobins, previously demonstrated by means of starch-gel electrophoresis. The different types of the other variable system have hitherto only been demonstrated by means of immuno-electrophoresis and also these serum types were found to be under genetical control (*Hirschfeld, Jonsson and Rasmuson* 1960) and not identical with the haptoglobins and other blood and serum groups investigated (*Hirschfeld* 1959 a and c, 1960 a, c and d, *Hirschfeld and Beckman* 1960).

At present the nature of these components is unknown and the symbol Gc (for group-specific components) has been suggested for the locus until the nature of this system is better known. The different serum types are called Gc 1–1, Gc 2–1 and Gc 2–2 depending on the existence of a single fast migrating group-specific component (Gc 1–1), the simultaneous presence of a fast and a slow component (Gc 2–1) or the presence of a single slow component (Gc 2–2) (*Hirschfeld and Beckman* 1960).

This paper deals with the distribution of the Gc-serum groups in a Lapp sample and some other Swedish samples from different parts of northern and central Sweden.

Between Lapps and other Swedes there are marked differences concerning many anthropological-genetical traits.

Blood group investigations of Norwegian Lapps (*Allison, Hartmann, Brendemoen and Mourant* 1952) and Swedish Lapps (*Allison, Broman, Mourant and Ryttinger*, 1956 *and Beckman, Broman, Jonsson and Mellbin* 1959) have shown that the Lapps have a very high A_2-frequency, a low frequency of Rh-negative individuals and relatively low M- and P-frequencies. There are some differences between Norwegian and Swedish Lapps concerning the frequencies of the B- and K-genes and between different Swedish Lapp populations there is a considerable heterogeneity. Thus between the Swedish Lapp groups there are significant variations concerning the AB0-, Rh-, MN- and P-blood group systems. In the northern Lapp group there is a high frequency of the C^w-gene of the Rh-system and in the southern group the A_2- and M-frequencies are higher.

2. Materials and Methods

A sample of 190 Lapp children was collected from the nomad schools of the county of Norrbotten. All individuals are from nomadic Lapp families. The blood groups (*Beckman, Broman, Jonsson and Mellbin* 1959) and the haptoglobin groups (*Beckman and Mellbin* 1960) of this sample have pre-

viously been examined. The sample includes related individuals to some extent (sibs) and the sera have been stored deep-frozen for some years.

Blood samples of 503 blood donors were collected from different hospitals in northern and middle Sweden.

One sample from Stockholm consists of females and males examined in paternity cases at the State Laboratory for Blood Group Serology.

In the routine testing of these sera, different anti-human immune sera prepared in rabbits and a few in horses were used.

The immunization procedure for obtaining these rabbit immune sera (*Proom* 1943) has been described in a previous communication (*Hirschfeld* 1960 b). Most of the sera were before use absorbed with a mixture of albumin and properdin fractions in order to absorb antibodies, which react with components other than the Gc-system in human serum. This technique has also been described previously (*Hirschfeld* 1960 a, c).

The immuno-electrophoretic separation was performed on object slides according to *Scheidegger* (1955) with some minor modifications (*Hirschfeld* 1960 b). In principle immuno-electrophoresis is carried out in two steps. First the sera to be investigated are electrophoretically separated in agar-gel. Thereafter precipitating antibodies are added in a longitudinal through cut parallel with the electrophoretic migration axis and situated at a certain distance from the electrophoretically separated components. The slides are incubated at 37° C for 16–20 hours. During this time the electrophoretically separated components (antigens) will diffuse towards the similarily diffusing immune serum (antibodies). Where the antigen and the corresponding antibody meet in the gel, a precipitate might appear. The electrophoretic position of this precipitate indicates the electrophoretic position of the corresponding antigen giving rise to this precipitate. Thus, the antibodies are the reactants by means of which the electrophoretic position of the corresponding antigen can be visualized in immuno-electrophoresis. The electrophoretic position of the Gc-precipitate in the immuno-electrophoretic pattern thus indicates the Gc-type to which this particular serum belongs.

The Gc-determinations were carried out on the native plates after 16–20 hours incubation. The agar slides were photographed on 15 $\times$36 mm film and repeated blind readings from the negatives were carried out. Only if a clear grouping was obtained by these independent readings was the result regarded as conclusive. In all other instances, repeated runs of the sera were performed until unambiguous results were obtained. In some instances it was necessary to use other immune sera in the subsequent runs in order to obtain a clear pattern. Most instances where the first determinations did

not give unambiguous results depend, however, on technical imperfections either in the immuno-electrophoretic separation or in the photographical documentation. Absence of Gc-groups or unsolved grouping difficulties have been met with in a few cases out of more than 2,000 different normal human sera being investigated in immuno-electrophoresis (including umbilical cord sera and sera from small children) and were found only in some sera which had been stored for several years. In those cases either no clear precipitates at all were found or a grossly abnormal immuno-electrophoretic pattern was obtained, in both instances making the identification of the Gc-groups unreliable.

3. Results

The frequencies of the Gc-groups in the Lapps are shown in table 1. It was possible to make a regional division into a northern and a southern group. The locations of these groups are shown on map 1.

There is a significant difference between the two regional samples ($\chi^2 = 5.24$, 1 d.f., $0.025 > P > 0.02$). The frequency of the Gc-gene is higher in the southern sample, there approaching 90% (Table 1). Differences between

Location of samples. The numerals refer to those of the samples in table 2. NL and SL – areas from which the north and south Lapp samples have been collected.

Table 1

Gc-groups and gene frequencies in the Swedish Lapps

Region		Gc-groups 1–1	2–1	2–2	Total	χ^2	Genes Gc^1	Gc^2
North (Karesuando, Jukkasjärvi)	obs.	71	41	1	113	3.56	81.0	19.0
	exp.	74.1	34.8	4.1				
South (Gällivare, Jokkmokk, Arjeplog)	obs.	61	16	0	77	1.04	89.6	10.4
	exp.	61.8	14.4	0.8				
Total	obs.	132	57	1	190	3.92	84.5	15.5
	exp.	135.6	49.8	4.6				
Unrelated individuals	obs.	60	18	1	79	0.073	87.3	12.7
	exp.	60.2	17.5	1.3				

Table 2

Gc-serum groups and gene frequencies in six different samples from northern and central Sweden

Region		Gc-groups 1–1	2–1	2–2	Total	χ^2	Genes, % Gc^1	Gc^2
1. Boden	obs.	55	41	10	106	0.336	71.2	28.8
	exp.	53.7	43.5	8.8				
2. Umeå	obs.	54	36	8	98	0.326	73.5	26.5
	exp.	52.9	38.2	6.9				
3. Sundsvall	obs.	51	38	11	100	1.368	70.0	30.0
	exp.	49.0	42.0	9.0				
4. Falun	obs.	55	44	2	101	4.145	76.2	23.8
	exp.	58.7	36.6	5.7				
5. Karlstad	obs.	68	28	2	98	0.205	83.7	16.3
	exp.	68.7	26.7	2.6				
6. Stockholm	obs.	51	37	9	97	0.362	71.6	28.4
	exp.	49.7	39.5	7.8				
Total	obs.	334	224	42	600	0.280	74.3	25.7
	exp.	331.23	229.14	39.63				

northern and southern Swedish Lapp populations have been found also concerning blood groups frequencies (cf. *Beckman, Broman, Jonsson and Mellbin*). Thus, in the south where the Gc^1-frequency is high, there are also higher frequencies of the A_2- and M-genes. In the north there are higher frequencies of the C^W- and P-genes.

The locations of the Swedish samples are shown on map. 1. The distribution of the groups and the gene frequencies are given in table 2. The agreement between observed and expected numbers is satisfactory except for one sample (Falun). The total Swedish material shows a significant heterogeneity ($\chi^2 = 13.38$, 5 d.f., $0.02 > P > 0.01$), depending mainly on the high frequency of the Gc^1-gene in the Karlstad sample. If the Karlstad sample is removed the rest of the material shows no significant heterogeneity ($\chi^2 = 2.43$, 4 d.f., $0.7 > P > 0.5$). There is no reason to believe that the deviating result found for the Karlstad sample depends on e.g. technical errors, since there is a good agreement between observed and expected numbers. Furthermore, the adjacent sample from Falun also shows some increase of the Gc^1-frequency. The frequency of the Gc^1-gene in the total Swedish material is 74 per cent, which is significantly lower than in the Lapps. A comparison of the sample of unrelated Lapps to the pooled Swedish material gives $\chi^2 = 12.56$, 1 d.f., $0.001 > P$.

It is typical for the Lapps that a very high frequency of the individuals with blood group A belong to the A_2-subgroup.

Table 3 shows the A_1-A_2 distribution among A-individuals of different Gc-groups. There is a significant correlation between the Gc 1–1 and A_2

Table 3

A_1-A_2 distribution among A-individuals of different Gc-groups (Gc 2–2 is unrepresented)

Gc-group		Blood group A_1	Blood group A_2	Total
Gc 1–1	obs.	10	63	73
	exp.	14.6	58.4	
Gc 2–1	obs.	13	29	42
	exp.	8.4	33.6	
Total		23	92	115

Heterogeneity: $\chi^2 = 4.96$, $0.05 > P > 0.02$

groups, which should be expected, since both high Gc^1- and A_2-frequencies are racial characters that distinguish the Lapps from the main Swedish population. This correlation is also consistent with the fact that the Gc^1- and A_2-frequencies are higher in the southern Lapp group compared to the northern group.

4. Discussion

The significant differences found between different populations in Sweden might be explained in several ways. As far as we know, no sampling bias which might affect the results have been operating in the different materials.

The sex and age distributions are, however, partly unknown in the samples. From a material consisting of mother-child samples and sera from males collected in connexion with paternity tests carried out at the State Institute for Blood Group Serology in Stockholm it is found that no significant differences appear between males, females and children (table 4).

The Lapp material was stored for a longer time and perhaps under more unfavourable conditions than the rest of the material. This had the practical consequence that Gc-typing was in some instances difficult to perform with the immune sera used routinely in this investigation. With a special immune serum which gives very clear-cut results but unfortunately is available in very small amounts (*Hirschfeld* 1959 a, fig. 4, 1960 b, fig. 14) no typing difficulties were found. Furthermore, the differences in distribution of Gc-types between the two Lapp samples (North and South) which were

Table 4

Distribution of Gc-groups in males, females and children

		Gc-groups			Total
		1–1	2–1	2–2	
Males		48	31	9	88
	%	54.6	35.2	10.2	
Females		299	219	38	556
	%	53.8	39.4	6.8	
Children		295	217	44	556
	%	53.1	39.0	7.9	

tested without knowledge of the regional origin of the individuals, seem to show that the differences found within the Lapp material are not affected by technical factors and thus the variations seem to be attributable to genetical differences (cf. also the correlation between the Gc^1- and A_2-genes).

Investigations hitherto carried out have also shown that the Gc-type is not changed by the storing of sera for more than 2 years at –20°C despite repeated thawings and freezings, storing at +4°C during at least one month, in room temperature for more than one week or at 56°C for one hour. Instead, sera which have been stored for long times give poor precipitate formation and thus the precipitates are sometimes impossible to register or grossly abnormal. Thus, in a few instances Gc-determinations have been impossible to carry out in sera stored under unsuitable conditions. This has, however, not been the case in any samples occurring in this study.

Sometimes it is necessary to carry out repeated tests with other immune sera in order to obtain reliable typing results. There may exist biologically determined, quantitative variations in the Gc- and other components, which might interact so as to give a poorly resolved pattern. More than 90% of this material has, however, been typed conclusively by the first examination.

The technical reproducibility of the typing has been checked by repeated runs of more than 240 different sera in blind tests. No differences in the Gc-types have been observed.

Two reference sera belonging to Gc-type 1–1 and 2–2 have been examined in more than 1,000 different immuno-electrophoretical tests with more than 100 different anti-human immune sera prepared in rabbits, horses, mice and sheep. In all cases the same typing results were obtained and the individual components of the Gc-system were found to be immunologically identical although electrophoretically different against all these immune sera. To further verify the determinations, 17 sera have been blindly determined at the University of Oslo (*Trond Reinskou*, personal communication) and at the State Institute for Blood Group Serology, Stockholm, employing the same technique but different immune sera. In all instances the same results were obtained.

In conclusion, it might be stated that the different results obtained concerning the Gc-distribution in different geographical and anthropological samples of human sera at the present moment cannot be attributed to technical factors affecting the Gc-determinations (employment of different immune sera or different storing conditions). Nor does it seem probable

that heterogeneity of the material as regards differences in sex or age distributions might affect the distribution of the Gc-types.

It therefore seems very probable that the differences in Gc-distribution found for different populations in northern and middle Sweden in fact indicate geographical and racial differences in the frequencies of the Gc-genes as has also been found for other genetically determined blood and serum systems. Thus Gc-groups may be looked upon as promising markers in anthropological research.

Furthermore, components which are immunologically similar to the Gc-system have also been found in monkeys (*Hirschfeld*, to be published). Therefore, the Gc-system may be of interest also in phylogenetical studies.

Summary

The distribution of the Gc-groups in geographically and racially different groups in northern and central Sweden has been studied. The frequency of the Gc^1-gene is significantly higher in Lapps as compared to other Swedish inhabitants. There are also significant variations between Lapp samples from the northern and southern parts of the county of Norrbotten, and between Swedish samples from different parts of northern and central Sweden.

The results are discussed from different technical and biological points of view and the conclusion is reached that these differences at the present standpoint of investigation cannot be explained by technical factors or sampling errors. It is concluded that the Gc-groups may be of interest in anthropological studies.

Zusammenfassung

Nach geographischen und rassischen Gesichtspunkten wurde die Verteilung der Gc-Gruppen bei Personen Nord- und Mittelschwedens untersucht. Die Häufigkeit des Gc^1-Gens ist signifikant höher bei den Lappen als bei anderen Einwohnern Schwedens. Ebenso wurden signifikante Abweichungen zwischen Lappen des nördlichen und südlichen Teiles der Provinz Norrbotten festgestellt sowie auch unter Schweden der verschiedenen Teile Nord- und Mittelschwedens. Die Werte werden von verschiedenen technischen und biologischen Gesichtspunkten aus diskutiert und mit dem Ergebnis, daß die Unterschiede im jetzigen Stand der Untersuchung nicht mit technischen Faktoren oder Irrtümern bei der Erfassung zu erklären sind.

Es wird weiterhin betont, daß die Gc-Gruppen für anthropologische Untersuchungen interessant sein könnten.

Résumé

Les auteurs ont étudié la répartition des groupes Gc dans des populations de races différentes et dans différentes parties de la Suède centrale et septentrionale. Ils ont trouvé une fréquence significativement supérieure du gène Gc^1 chez les Lapons par rapport aux autres habitants de la Suède. Il existe aussi des variations significatives entre les échantillons de Lapons vivant dans les régions septentrionales et méridionales du comté de Norrbotten, et les échantillons suédois de diverses parties de la Suède septentrionale et centrale.

Les résultats sont discutés sous différents aspects techniques et biologiques et les auteurs arrivent à la conclusion que ces différences, à l'état actuel des recherches, ne s'expliquent pas par des facteurs techniques ou par des erreurs d'échantillonnage. On en conclut que ces groupes Gc peuvent présenter un intérêt dans des études anthropologiques.

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Authors' addresses: Dr. J. Hirschfeld, Statens Rättskemiska Laboratorium, *Stockholm* 60, Dr. L. Beckman, Institutionen för Medicinsk Genetik, V. Ågatan 24, *Uppsala* (Sweden).

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From the University Institute for Human Genetics, Copenhagen

Two New Pathological Concepts

THE CHROMOSOMAL DISEASES AND THE GLOBAL DISEASES

By TAGE KEMP

Whenever the question is raised about the results achieved so far within medical science or within a certain branch of this, the problem which naturally suggests itself is whether new diseases have occurred within the field concerned, and, if so, whether we can describe and define these diseases as well as establish their cause and elucidate their development and course.

It is a well-known fact that new diseases occasionally appear. Not previously known causes of illness are discovered, or certain diseases are found to develop otherwise than previously described, thus changing completely in character. Further, we may find that familiar diseases become classifiable into new and totally different groups or categories.

On the basis of the experience gained and the observations made within recent years I propose to introduce two new groups or concepts of diseases, *viz. the chromosomal diseases* and *the global diseases*. Next, there may be reason to compare these two groups of diseases to establish their points of resemblance and their differences.

The chromosomal diseases are determined by deviations from the normal in the chromosomal conditions, demonstrable only by microscopy.

The chromosomes, or nuclear filaments, are very small, often filiform formations or bodies occurring in the cells of man, animals, and plants. The hereditary factors or genes are located on the chromosomes. During cell division the nucleus of the cell is split into a certain number of chromosomes. The number is constant within each species, but varies from one species to another, thus contributing towards characterizing the species. In man the normal number of chromosomes is 46 in both sexes. However, in the mature sex cells, whether egg cells or sperm cells, this number is reduced to half,

i.e. 23. In the female sex cells one of the 23 chromosomes is an X-chromosome, while in the male sex cells one of the 23 chromosomes is either an X-chromosome or a Y-chromosome. Thus, half of the male sex cells, the spermatozoa, contain an X-chromosome and the other half a Y-chromosome.

At the act of fertilisation a new individual arises by fusion of a sperm cell with an egg cell. This individual likewise gets 46 chromosomes, 44 ordinary chromosomes plus 2 sex chromosomes; in the male 44 + X + Y and in the female 44 + X + X, in other words normally 46 in both sexes. The X-chromosome is the female sex chromosome, while the Y-chromosome is that determining the male sex.

The chromosomal diseases are, as stated, determined by deviations of the chromosomes from the normal with regard to number, shape, and size, as well as their locations in relation to each other. In addition, the number of chromosome sets as well as the ratio between X- and Y-chromosomes and between the other chromosomes may possibly be abnormal.

Accordingly, the concept of chromosomal diseases is not identical with that of hereditary diseases, the latter being far more comprehensive. The hereditary diseases depend, it is true, on changes in the hereditary factors located in linear arrangement on the chromosomes, but these factors are generally invisible even when highly magnified, in fact even under electron microscopes.

The chromosomal diseases thus constitute a subgroup within the group of hereditary diseases. We do not know the genes provoking these diseases, but the diseases have been observed to be associated with changes of the chromosomes, or, perhaps more correctly, the chromosome picture in the affected patients. Such changes are visible under the microscope. The chromosomal diseases have certain features in common. Many of these patients have intelligence defects, or may even be characterized as proper mental defectives. Further, such patients often present physical deformities, e.g. congenital heart defects, development of female mammary glands in men, and the like. Patients suffering from chromosomal diseases often present abnormal development of their sexual character. They may be hermaphrodites. There may be deficient or abnormal development of the sexual glands, the male as well as the female, and these anomalies are often related to deviations in the number of X- and Y-chromosomes. Some patients with chromosomal diseases may thus have two X-chromosomes and one Y-chromosome, and they may have hermaphroditic character, possibly associated with dwarfism.

Other such patients are marked by deficient development of the sexual characteristics, manifesting itself by a special defect of the sexual glands and often due to the number of sex chromosomes being too small. For instance, in some patients who have only one sex chromosome, e.g., an X-chromosome but no Y-chromosome, a defective sexual development is seen. This doubtless manifests itself primarily by a deficiency of sex chromosomes, but is also reflected in an altered total chromosome number in the individuals concerned. Most humans have, as stated, 22 pairs of ordinary chromosomes in addition to their sex chromosomes. If, then, they have only one sex chromosome, their total number of chromosomes will amount to 45. If there are three sex chromosomes, the total chromosome number will be 47. If these three sex chromosomes comprise two X- and one Y-chromosome, the patient will get hermaphroditic characteristics under the influence of the interaction of the X- and Y-chromosomes.

If, on the other hand, the three chromosomes are all X-chromosomes, the individual concerned will be marked by the action of the three X-chromosomes and have a particularly female character. Such persons have been called superfeminine. This phenomenon is plainly seen in experimental animals, e.g. the fruit fly, so commonly used in genetic experiments. In man the condition is to a greater extent marked by the general disorder of the function and interaction of the sex chromosomes. The result is characterized more by a general deficient sexual development than by occurrence of intermediate sexual forms.

In connection with these experiments I may mention some interesting observations made as bold conjectures rather than through systematic scientific experiments. Some time ago I attended a meeting in London together with a number of physicians and other scientists from many different countries. They had all within the past few years devoted themselves specially to the study of the chromosomal diseases.

In particular they had noticed that among the examined patients with chromosomal diseases or among their relatives there were many who, with a pinch of salt, must be characterized as "beauty queens" or "world champions".

The condition of these individuals was probably open to the interpretation that the admixture of the factors of the other sex had a special effect in question; in other words, a minor admixture of male factors in women might have a favourable effect corresponding with the current taste. Slender, muscular figures were seen, agreeing with the present ideal of women and giving to those concerned a stamp of "sports stars". Some good

might, in other words, come of the chromosomal diseases, when the factors concerned were present in a mild degree and in a suitable mixture.

However, this hypothesis should not be taken as more than a somewhat superficial view based on sporadic observations. But it suggests to us the importance of the chromosomal element in the entire personal development, the development of the individual character.

This manifests itself particularly clearly in the human beings suffering from the proper chromosomal diseases, where the mental type as well as the physical character become altered by the intelligence defect and by the other special signs and symptoms. Some of the diseases have been known for some length of time, but their aetiologies have been obscure. As an instance of these we may mention mongolian idiocy, or the mongolism the occurrence of which is related to the presence of an extra chromosome (i.e., a total of 47 chromosomes in mongolian idiots). This supernumerary chromosome does not belong to the sex chromosomes. Other diseases having a special character may also be mentioned. The great majority are congenital, affect the whole organism, and are related to chromosomal defects or anomalies. (For further literature with details, reference may be made to Tage Kemp: *Arv og Kaar*, 2nd enlarged edition, Munksgård, Copenhagen 1960).

After a more intense study of the human chromosomes by quite modern methods of cell analyses, some characteristic clinical pictures related to abnormal chromosome numbers or chromosome pictures were first described in humans in 1956. In man a number of X- or Y-linked genes have for some time been known to be located on the X- or the Y-chromosome respectively. But it has not been observed previously in man that certain diseases or abnormal states occur in association with chromosome numbers deviating from the normal or with chromosome deformations.

Our knowledge regarding the chromosomal diseases can thus be said to date from the year 1956. They constitute an important group of diseases because they are very severe, being highly disabling or causing the patients other harm. It is no exaggeration to say that they mark the patients throughout life and often prove fatal. These diseases are by no means rare, but we are not yet able to state the exact number.

It has been mentioned that the group of diseases was first discovered few years ago, but it is probably a category which has existed for many years, perhaps thousands of years and through countless generations, before it was recognized. Some modern workers claim, however, that chromosomal diseases have become a common occurrence nowadays owing to the intense use of atomic energy within recent years.

In an attempt to throw further light on this question I shall proceed to give an account ot the other group of diseases included in the present talk, namely, that of the *global* diseases.

The global diseases are such as may develop in consequence of the falling of radioactive substances produced by explosions, so far most often test explosions, of atomic bombs and nuclear weapons. The radioactive fall-out descends on the globe from the stratosphere or even more distant spheres. It spreads over different parts of the globe. That is why the diseases have been called global.

From a medical point of view our knowledge of the signs and symptoms of the global diseases originate from an analysis of the after-effects of the explosions of the atomic bombs that were dropped at Hiroshima and Nagasaki in the autumn of 1945. There was here a favourable opportunity of studying these after-effects, because more than 300 000 died in consequence of the explosions, either in direct relation to the explosions or in the course of the following years owing to the delayed effects.

The artificial radioactive radiation may come from many sources. Since the discovery of the X-rays in 1895, X-rays and radium as well as other radioactive substances have been used to a steadily increasing extent, especially within medicine for diagnosis as well as for treatment. No small quantities of ionising rays are thus induced into the human body. Some of these rays will reach the sexual glands. They may do harm here, especially in cases of radiation of the pelvis and abdomen of patients of the procreative age or younger, or if large, repeated radiation doses are given on other parts or regions of the body. Unchecked use of ionising radiation within medicine is therefore, naturally, inadvisable. Such treatment should only be given when urgently necessary, and all protective measures should then be carefully taken, such as covering or screening of the sexual glands with lead plates or the like.

The physicians have, of course, been aware of this fact for many years. Industrial employment of ionising radiation may also cause people to be exposed to dangerous irradiation. This is a factor to be considered now that, during the past 10 to 20 years, atomic energy has become increasingly used for various purposes. It always involves a certain risk to utilize natural forces for technical purposes of different kinds. This is particularly true of atomic energy, not the least so because of the potential genetic risk.

The military use of atomic energy must, however, be supposed to be by far the most dangerous, particularly because it largely evades control. As stated, atomic bombs were used twice in 1945 for direct military purposes,

and tests with atomic and hydrogen bombs were undertaken regularly until such were stopped by agreement some years ago. The agreement was broken by France in February 1960, and a few power-seeking nations in America, Asia, and Europe are still anxious to belong to the countries disposing of atomic bombs.

In certain tracts of America and in Japan, among others, the radioactive fall-out has caused considerable rises of the mean radiation level. The region exposed to radioactive fall-out after use of nuclear weapons also depends on the direction and force of the wind at up to 25 km or higher above the earth within the area of explosion. All these facts have by no means been clarified as yet, but they call for caution and reserve with regard to undertaking test explosions.

We may distinguish between the physiological and the genetic effect of ionising radiation. The former comprises a fairly prompt effect occurring within a few hours or days and manifesting itself by general fatigue and malaise, as well as delayed or tardive effects, which may set in at different times after the irradiation within a period of many years. The manifestations may here be loss of hair, premature greying of the hair, burns of skin and tissue which have difficulty in healing up. The irradiation may also give rise to changes in the blood, such as anaemias and deficiency of leucocytes, i.e. granular, white blood cells, or leukaemia, which is the reverse, being a cancer-like disease with an excess of white blood cells. Further, malignant tumours may be provoked, and opacity of the lens of the eye, a kind of cataract, may develop.

The radioactivity is bound to small particles, e.g. dust particles, which have a slow falling rate. The fall-out consists of a large number of radioactive substances of varying longevity. Among these are strontium and caesium, whose contribution to the radioactivity is reduced by no more than 50 per cent in the course of about 30 years. In the Scandinavian countries some interesting observations were made regarding the radioactive fall-out resulting from test explosions over the Arctic Ocean in the autumn of 1958. Considerable amounts of fission products were then thrown up into higher strata of air. The amounts increased until 6 months after the explosions, then remained unchanged till about 9 months after, when it decreased to rather insignificant quantities in the course of the last 3 months of the first year. In October, 1959 the amounts were from one-tenth to one-hundreth of those measured in May, 1959.

These clear observations plainly show how the fall-out ceases rather soon after the conclusion of the test explosions. The most effective measure

against the dangerous radioactive fall-out will therefore be to discontinue the test explosions, in order to quickly and definitely stop the radioactive fall-out. This proves the decisive importance of stopping the atomic weapon tests, a measure which we are all hoping to see fulfilled, and which many humane personalities aim at having carried through permanently.

To-day we may be justified in regarding the peaceful use of atomic energy as an undertaking of great promise, which opens out vast prospects and perspectives.

However, one thing we must all realize: the use of atomic energy for test explosions for military purposes should be stopped and the sooner the better. Nuclear warfare may have unpredictable genetic consequences for mankind through future generations.

Summary

On the basis of the experience gained and the observations made within recent years I propose to introduce two new groups or concepts of diseases, *viz.* the chromosomal diseases and the global diseases.

The chromosomal diseases are determined by deviations from the normal in the chromosomal conditions, demonstrable only by microscopy.

During cell division the nucleus of the cell is split into a certain number of chromosomes. The number is constant within each species, but varies from one species to another, thus contributing towards characterizing the species.

Accordingly, the concept of chromosomal diseases is not identical with that of hereditary diseases, the latter being far more comprehensive.

The chromosomal diseases have certain features in common. Many of these patients have intelligence defects, or may even be characterized as proper mental defectives. Further, such patients often present physical deformities. Patients suffering from the chromosomal diseases often present abnormal development of their sexual character.

The global diseases are such as may develop in consequence of the falling of radioactive substances produced by explosions, most often so far test explosions of atomic bombs and nuclear weapons. The radioactive fall-out descends on the globe from the stratosphere or even more distant spheres. It spreads over different parts of the globe. That is why the diseases have been called global.

Zusammenfassung

Auf Grund von Erfahrungen und Beobachtungen der letzten Jahre möchte ich zwei neue Gruppen oder Begriffe von Krankheiten einführen: Die chromosomalen und die globalen Krankheiten. Die chromosomalen Krankheiten beruhen auf Veränderungen in den Chromosomen, die jedoch nur mikroskopisch nachweisbar sind. Während der Zellteilung wird der Zellkern in eine bestimmte Anzahl von Chromosomen zerlegt. Ihre Zahl ist in jeder Art konstant, unterscheidet sich jedoch bei den einzelnen Arten und bietet damit ein charakteristisches Unterscheidungsmerkmal zwischen den einzelnen Arten. Demzufolge ist der Begriff der chromosomalen Krankheiten nicht mit dem der Erbkrankheit gleichzusetzen; denn der letztere ist weitaus umfassender.

Die chromosomalen Krankheiten zeigen untereinander gewisse Ähnlichkeiten, viele der Patienten weisen Intelligenzdefekte auf oder können sogar als schwachsinnig bezeichnet werden. Darüber hinaus zeigen solche Patienten auch oft körperliche Mißbildungen. Bei Patienten mit chromosomalen Krankheiten beobachtet man auch häufig eine abnorme sexuelle Entwicklung.

Globale Krankheiten sind solche, die zum Beispiel durch radioaktiven Niederschlag bei Explosionen entstehen, bisher vor allem durch Atombomben-Testexplosionen und nukleare Waffen. Der radioaktive Niederschlag sinkt von der Stratosphäre oder noch ferneren Sphären auf die Erde und verbreitet sich über die verschiedenen Gebiete. Deshalb spricht man von globalen Krankheiten.

Résumé

En se basant sur les expériences et observations de ces dernières années l'auteur propose d'introduire deux nouveaux groupes ou catégories de maladies à savoir les maladies chromosomiques et «terrestres».

Les maladies chromosomiques sont dues à des anomalies chromosomiques qui peuvent être décelées au microscope.

Pendant la division cellulaire, le noyau se décompose en un certain nombre de chromosomes. Ce nombre est constant pour chaque espèce et varie d'une espèce à l'autre, par conséquent, il caractérise l'espèce.

Le terme de maladie chromosomique n'est pas identique à celui de maladie héréditaire, ce dernier ayant un sens beaucoup plus étendu.

Les maladies chromosomiques ont certains caractères en commun. De nombreux malades présentent une intelligence déficiente ou même une vraie maladie mentale. En outre, on rencontre chez eux souvent des anomalies constitutionnelles. Les patients atteints d'une maladie chromosomique présentent souvent un développement anormal de leur caractère sexuel.

Les maladies «terrestres» se développent à la suite d'une pluie de substances radioactives produite par des explosions, le plus souvent à la suite d'essais de bombes atomiques ou des armes nucléaires. La pluie radioactive descend de la stratosphère ou même de sphères plus éloignées. Elle peut s'étendre sur différentes parties du globe terrestre. Ces maladies sont appelées maladies «terrestres».

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Author's address: Professor Tage Kemp, Universitetets Arvebiologiske Institut, 14 Tagensvej, *Copenhagen N* (Denmark).

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From the Laboratory of Physiological Chemistry, University of Amsterdam

A GENETIC INVESTIGATION ARISING FROM TWO CASES OF FAVISM

By T. L. OEI

Introduction

Favism, a haemolytic reaction after eating broad beans *(Vicia faba)*, occurs quite frequently among Mediterranean populations. According to *Szeinberg and Sheba* (1958), the first definite reports of favism appeared earlier than the 5th century B.C. and they suggest that a connection exists between the syndrome and the prohibition of the eating of beans in ancient Egypt and the abstinence of the Pythagoreans from this food.

Recent investigations, which have been extensively reviewed by *Beutler* (1958), show that the erythrocytes of patients with a haemolytic anaemia caused by the ingestion of the broad bean or certain drugs, such as primaquine, are characterized by a decreased stability of erythrocyte glutathione to treatment with acetylphenylhydrazine *in vitro* (*Beutler*, 1956), and by a decreased activity of glucose 6-phosphate dehydrogenase (*Carson, Flanagan, Ickes and Alving*, 1956).

Although little is known about the relationship between these two biochemical abnormalities and the haemolytic anaemia, it seems likely that the decreased glutathione stability is a direct consequence of the diminished enzyme activity, since this enzyme is responsible both directly and indirectly for the supply of TPNH which is necessary for the reduction of GSSG to GSH.

1. glucose 6-phosphate + TPN^+ $\xrightarrow{\text{(glucose 6-phosphate dehydrogenase)}}$ 6-phosphogluconolactone + TPNH + H^+

2. 6-phosphogluconolactone + H_2O $\xrightarrow{\text{(lactonase)}}$ 6-phosphogluconic acid

Abbreviations: TPN^+, TPNH, oxidized and reduced triphosphospyridine nucleotide; GSH, GSSG, glutathione and oxidized glutathione; Tris, tris(hydroxymethyl)aminomethane.

3. 6-phosphogluconic acid + TPN^+ —(6-phosphogluconic acid dehydrogenase)→ ribulose 5-phosphate + TPNH + H^+ + CO_2

4. TPNH + GSSG + H^+ —(GSSG reductase)→ 2 GSH + TPN^+

An impaired activity of the enzyme catalysing reaction (1) will clearly decrease the ability of the erythrocyte to reduce GSSG. Experiments of *Keilin and Hartree* (1946), *Fegler* (1952), *Benesch and Benesch* (1954) and *Sheets, Hamilton and Degowin* (1956) suggest that there is an increased tendency for erythrocytes to haemolyse when the GSH content is decreased.

Extensive investigations by *Childs, Zinkham, Browne, Krimbo and Torbert* (1958) and *Szeinberg, Sheba and Adam* (1958), using the glutathione-stability test, and by *Gross, Hurwitz and Marks* (1958) and *Larizza, Brunetti and Grignani* (1960), who measured both the glutathione stability and the activity of the glucose 6-phosphate dehydrogenase, have clearly shown that the biochemical abnormalities are familial, and suggest strongly that they are due to a sex-linked mutant gene which in the female heterozygote carrier is incompletely dominant and is variably expressed. In a recent review, *Childs and Zinkham* (1959) have drawn attention to the difficulty of discriminating the female heterozygote from the two homozygotes, and have suggested that, in future, attention should be concentrated on family groups rather than upon populations of unrelated individuals.

A boy, now 9 years old, described as a case of favism by *Bolt* in 1955, and a 70 years old woman from the same family who recently suffered an attack of haemolytic anaemia after eating broad beans formed the starting point of the present investigation. The activity of the erythrocyte glucose 6-phosphate dehydrogenase in 100 members of this family living in the village of Sloten in West Amsterdam was measured. With the exception of the two cases already mentioned, none of the subjects is known to have suffered from haemolytic anaemia.

Methods

2 ml blood were collected in heparin by venipuncture and immediately placed in ice. The erythrocytes were collected by centrifuging for 3 min at 3000 rev./min, washed twice with 10 ml of isotonic KCl, and suspended in an approx. equal volume of isotonic KCl. The haemoglobin content of the suspension was determined by adding 0.02 ml to 6 ml water, followed by 1 drop 10% NH_3. The absorbancy was measured at 540 mμ and the haemoglobin concentration calculated on the basis of an absorbancy of 940 cm^2.g haemoglobin. The remainder of the suspension was haemolysed by holding at -20^0 overnight.

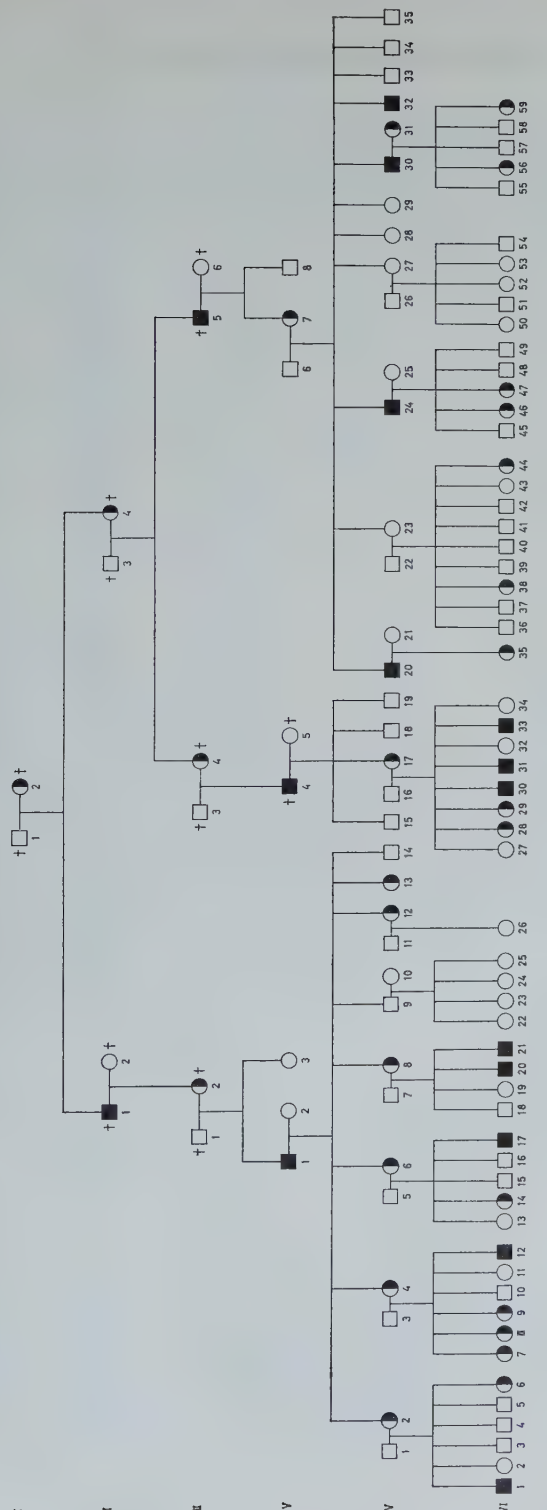

Fig. 1

Pedigree of family investigated. □, normal male (glucose 6-phosphate dehydrogenase, $> 10\ \Delta$ A/min/g haemoglobin); ■, deficient male (< 3); ○, normal female (> 11); ◑, intermediate female (between 3 and 11). All living members of the family shown in this pedigree were investigated. The most probable phenotype of the deceased members (†) was deduced from those of their descendants, as described in the text.

Table 1

Enzyme activities of all subjects investigated

Member	Generation					
	I	II	III	IV	V	VI
1	–	–	–	1.7	13.9	1.5
2	–	–	–	19.3	4.1	12.3
3		–	–	11.3	14.3	14.4
4		–	–	–	10.2	15.7
5			–	–	14.9	15.1
6			–	12.4	7.5	9.1
7				7.8	15.1	8.6
8				13.0	10.8	8.8
9					12.3	8.3
10					14.8	13.4
11					13.6	13.6
12					7.1	2.7
13					8.4	12.9
14					11.8	6.4
15					14.9	17.8
16					12.7	16.0
17					6.9	1.7
18					14.6	20.8
19					11.7	16.1
20					1.2	2.2
21					12.0	2.5
22					12.4	15.4
23					11.1	14.8
24					1.5	15.4
25					11.8	14.8
26					15.4	15.4
27					12.4	11.1
28					16.1	7.6
29					14.3	7.8
30					2.0	0.7
31					10.8	1.2
32					1.9	13.5
33					13.0	2.2
34					14.8	12.7
35					12.0	9.8
36						10.8
37						11.6
38						10.6
39						13.5
40						12.1
41						11.3

Member	Generation					
	I	II	III	IV	V	VI
42						12.6
43						14.2
44						10.7
45						13.1
46						7.6
47						4.8
48						13.1
49						13.0
50						13.1
51						13.5
52						16.4
53						15.0
54						13.0
55						12.3
56						10.6
57						13.0
58						13.8
59						10.3

1 vol. of the haemolysate was diluted with 3 vol. ice-cold distilled water, and the glucose 6-phosphate dehydrogenase activity determined essentially as described by *Zinkham, Lenhard and Childs* (1958). 0.1 ml of the diluted haemolysate was added to 2.4 ml of a reaction mixture containing (final concn. after adding the haemolysate) 0.05 M Tris-HCl buffer (pH 7.6), 0.02 M $MgCl_2$, 4 mM glucose 6-phosphate, 0.092 mM TPN^+. The absorbancy at 340 mμ was measured every 30 sec for 5–10 min, using as reference cell 0.1 ml haemolysate added to 2.4 ml 0.05 M Tris-HCl buffer. The temperature of the reaction mixture was measured before and after the reaction, and the mean temperature used to convert the measured reaction velocity to 25°, on the assumption that $Q_{10} = 2$. The activity is expressed as ΔA/min/g haemoglobin.

In order to test the reproducibility of the method, the entire procedure was carried out on each of five portions of the same blood sample. The values for ΔA/min/g haemoglobin were 10.3, 10.0, 10.5, 10.1 and 10.3, respectively. Most of the values given in this paper were a single determination.

Results

The results are summarized in Fig. 1 in the form of a pedigree, which also includes those members, now dead, who form important links between different members of the family. The glucose 6-phosphate dehydrogenase activities are listed in Table 1. All the members of the generations V and VI in the pedigree were investigated.

Figs. 2a (males) and 2b (females) describe the frequency distribution of the enzyme activities. The results are, in general, in good agreement with those found by *Childs et al.* (1958) for the glutathione stability test and by *Larizza et al.* (1960) for the glucose 6-phosphate dehydrogenase. The values for the males show two clearly separated peaks, a group with activities lying between 0 and 3 which we shall refer to as "deficient", and a group with activities between 10 and 21, which are normal. The peaks were found at 1–2 and 13–14, respectively.

On the other hand, the values for the females do not fall into clearly separated groups, varying almost continuously between 4 and 20. No values below 4, characteristic of deficient males, were found. Significantly,

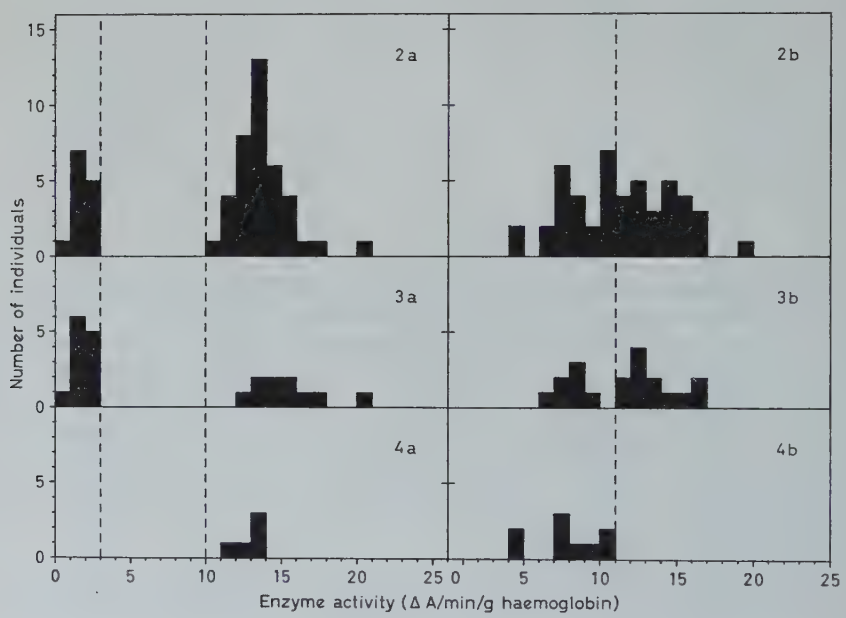

Fig. 2

Frequency distribution of all males (Fig. 2a) and females (Fig. 2b) in the family.

Fig. 3

Frequency distribution of all males (Fig. 3a) and females (Fig. 3b) arising from the mating normal father × intermediate mother.

Fig. 4

Frequency distribution of all males (Fig. 4a) and females (Fig. 4b) arising from the mating deficient father × normal mother.

Table 2

Enzyme activities of children from various matings

Mating (father × mother)	Number of families	Sons		Daughters		
		deficient	normal	deficient	intermediate	normal
normal × normal	3	0	8	0	2	8
normal × intermediate	7	12	10	0	7	12
deficient × normal	3	0	5	0	9	0
deficient × intermediate	1	0	3	0	2	0
	14	12	26	0	20	20

the region between 4 and 11, which was represented by only one value (10.8) in the males, was occupied by 23 of the 52 females. We shall refer to the females in this region as "intermediate".

The 100 members of the family investigated represent 14 matings with their offspring. In Table 2 are grouped the various mating combinations studied, together with the enzyme analyses of the offspring. Figs. 3a (males) and 3b (females) show the distribution of the values of children arising from the mating normal father × intermediate mother, and Figs. 4a and 4b for the mating deficient father × normal mother.

Table 3 summarizes all the results according to sex and enzyme activity.

Discussion

The following conclusions can be drawn from the results presented

1. No intermediate values are found in males.

2. All 8 sons of deficient fathers are normal and all 11 daughters intermediate.

3. It was possible to study both parents, in the case of 12 of the 13 deficient males. All 7 fathers were normal and all 7 mothers intermediate.

4. Out of 22 sons of the mating of 7 intermediate mothers and 7 normal fathers, 12 were deficient and 10 normal. Out of 19 daughters, 7 were intermediate and 12 normal.

It is clear that the enzyme abnormality cannot be transmitted from father to son. It is transmitted from the mother to half of her sons and daughters and from the father to all his daughters. This is strong support for the postulate that the enzyme abnormality is inherited in a sex-linked fashion, that the abnormal gene is incompletely dominant, and that the deficient males, intermediate females and deficient females represent the

Table 3

Distribution of enzyme activities according to sex of all individuals examined

Enzyme activity	Males		Females	
	no.	%	no.	%
Deficient	13	25	0	0
Intermediate	0	0	23	48
Normal	39	75	25	52
	52	100	48	100

hemizygote, heterozygote and homozygote, respectively. This is further supported by two other observations:

1. There were 7 matings of the type normal father and intermediate mother against 3 matings of deficient father and normal mother. This is close to the 2:1 ratio that can be expected when a random mating is assumed.

2. Of the 28 abnormal (deficient + intermediate) values found in the children of the matings normal father × intermediate mother or deficient father × normal mother, 19 are derived from the mother and 9 from the father. This is close to the expected 2:1 ratio.

An examination of the pedigree reveals that in only one mating (V 22 × V 23) are the results apparently in conflict with the expected pattern. Although both parents are classified as normal, there were besides 6 normal sons and 1 normal daughter 2 intermediate daughters (these are the two in the first line of Table 2). However, the values used for the classification are very close to 11, which we have chosen to separate normal from intermediate females. The mother had an activity of 11.1 which must be classified as normal, but perhaps was really intermediate. In that case, however, the absence of a deficient son is unexpected although not impossible. More probably, the two daughters classified as intermediate were in reality normal, since their activities were 10.6 and 10.7, respectively.

The mating V 30 × V 31 was, according to the classification, deficient father × intermediate mother, which would be expected to yield some deficient daughters as well as sons. In fact, both daughters were intermediate and the three sons normal. The numbers are too small to be regarded as neccessarily inconsistent with expectations. However, it is possible that the mother, classified as intermediate on the basis of an activity of 10.8, is in reality normal.

The distributions shown in Figs. 3a and 3b agree closely with the expected equal numbers of deficient and normal sons (12:10), but there are rather less intermediate than normal daughters (7:12). Possibly some of the daughters classified as normal were, in reality, intermediate.

These examples illustrate that it is not possible, with complete certainty, to separate the female heterozygote from the normal on the basis of the enzyme activity, as indeed was to be expected from the distribution curve shown in Fig. 2b.

If it is accepted that the inheritance of the enzyme abnormality is sex-linked, we can draw conclusions concerning the deceased members of the family. IV 1, a deficient male, must have inherited the abnormality from his mother III 2. Since his sister (IV 3) is normal, his father (III 1) must have been normal and his mother (III 2) could not have been a homozygote deficient; thus she must have been heterozygote. III 2 could have inherited the abnormality from her father (II 1) or her mother (II 2). The presence of the abnormality in the descendents of a sister (II 4) of II 1 makes it probable that the latter was deficient. No conclusion can be drawn about the mother II 2. II 1 must have inherited the abnormality from his mother I 2, who must have been either homozygote deficient or heterozygote.

V 17, a female heterozygote, could have inherited the abnormality either from her father (IV 4) or mother (IV 5), but since her brothers (V 15, V 18 and V 19) were normal, the mother is the less likely possibility, although not impossible. In any case, she could not have been a homozygote deficient. The abnormality found in the descendents of the brother (III 5) of the mother (III 4) of IV 4 strongly supports the choice of IV 4 as the source of the abnormality in V 17. He must have inherited this abnormality from his mother III 4, who must have been at least heterozygote and was possibly a deficient homozygote.

The abnormality in IV 7, a heterozygote female, was probably derived from her father (III 5), a brother of III 4. Since her brother (IV 8) is normal, her mother could not, in any case, have been a deficient homozygote.

A heterozygote III 4 and a hemizygote III 5 require at least a heterozygote mother (II 4). III 4 would have been a homozygote deficient,only if her father II 3 had been a hemizygote. Similarly, a heterozygote I 2 is sufficient to explain the hemizygote II 1 and a heterozygote II 4. A homozygote II 4 would require that the father I 1 was also deficient. The minimum hypothesis, and the most probable since it requires only one original source of the abnormality, is that the first mother (I 2) in the pedigree was a heterozygote.

We have been unable to obtain any indication that the genetic abnormality was imported from the Mediterranean Sea region, but that cannot be excluded. II 3 and III 3 were of German origin, but II 3 could have been a source of an abnormality only in III 4 and her descendents, while an abnormality in III 3 would have had no effect on any of the subjects studied in this work.

The high fertility of the family investigated is noteworthy. I 1 × I 2 had 10 children; II 1 × II 2, 6; II 3 × II 4, 12; III 1 × III 2, 9; III 3 × III 4, 13; III 5 × III 6, 11. Since, out of the 13 hemizygote males and 23 heterozygote females only one boy (VI 20), the case described by *Bolt* (1955), and a woman (IV 7) had, to our knowledge, ever had a haemolytic reaction, it appears that the enzyme abnormality has little serious effect. So far as perpetuation of the family is concerned, any disadvantage is compensated by the high fertility. The large number of descendents of I 2 offers further possibilities of a continuance of the genetic research, which is being pursued.

Summary

Two cases of favism in a family living in a village near Amsterdam led to an investigation of the glucose 6-phosphate dehydrogenase activity in the erythrocytes of 100 members of the family. Out of 52 males and 48 females, 13 deficient males and 23 females with intermediate values were found. The pattern of inheritance is in good agreement with previous suggestions that the enzyme abnormality is due to an incompletely dominant sex-linked mutant gene. The high fertility of the members of the family has contributed to the spreading of the abnormality.

Zusammenfassung

Zwei Fälle von Favismus in einer holländischen Familie (Dorf in der Nähe Amsterdams) führten zu der Untersuchung der Glucose-6-Phosphat-Dehydrogenase-Aktivität der Erythrocyten bei 100 Angehörigen der Familie. Unter 52 männlichen und 48 weiblichen Personen fand man 13 männliche, die den Defekt aufwiesen und 23 weibliche mit intermediären Werten. Dadurch werden frühere Vermutungen über den Erbgang bestätigt: Die Enzymanomalie wird durch ein unvollständig dominantes, x-chromosomales Gen hervorgerufen. Die sehr große Fruchtbarkeit der Mitglieder dieser Familie trug zu der weiten Verbreitung der Krankheit bei.

Résumé

Deux cas de favisme dans une famille vivant dans un village près d'Amsterdam ont entraîné une recherche sur l'activité du glucose-6-phosphate-déhydrogénase dans les globules rouges de 100 membres de la famille. Sur 52 hommes et 48 femmes, l'auteur a trouvé des carences chez 13 hommes et des valeurs intermédiaires chez 23 femmes.

Le mode d'hérédité est tout à fait conforme à l'hypothèse que l'anomalie enzymatique est due à un gène muté, lié au sexe et incomplètement dominant. Le haut degré de fertilité de la famille a contribué à la dispersion de l'anomalie.

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Author's address: Drs. T. L. Oei, Laboratorium voor Fysiologische Chemie, J. D. Meijerplein 3, *Amsterdam-C* (Netherlands)

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From the Department of Endocrinology of the First Medical Clinic
Hospital das Clinicas and the Laboratory of Human Genetics
Faculty of Medicine, University of São Paulo, Brazil

THE LAURENCE-MOON SYNDROME, A PEDIGREE WITH UNCOMMON FEATURES

By NELSON LEON, ANTÔNIO DA SILVA COELHO NETO, P. H. SALDANHA, CELSO A. DE CARVALHO and A. B. DE ULHÔA CINTRA

Hypogenitalism, obesity, mental retardation, retinitis pigmentosa and polydactyly constitute the cardinal symptoms of a congenital syndrome which should be named after *Laurence and Moon* (1866), the original discoverers of the disease. Many of the affected individuals reported, including the first ones, lacked one or another of the characteristics of the complete pentad or revealed the presence of other anomalies such as shortness of stature, deafness, diabetes mellitus, brachydactyly, syndactyly, skull defects, microphtalmia, etc., some of them probably due to the high frequency of consanguinity encountered in the families of the affected. According to *Falls* (1953), obesity and polydactyly are the most characteristic features of the disease in childhood. Other authors such as *Warkany* (1937), *Burn* (1950), *Alström et al.* (1959) find obesity and hypogenitalism occurred more often as characteristic features of the entity. *Alström et al.* (1959) believe that, as a rule, "the simultaneous occurrence of at least three symptoms is required for the diagnosis". The complete syndrome occurred according to the same authors in 1 out of 14 cases where it was combined with impaired hearing. *Blumel and Kniker* (1959), reviewing the 65 cases published in the literature since 1949, found that the incidence of the symptoms appears as follows: obesity 83%, mental deficiency 80%, polydactyly 75%, retinitis pigmentosa 68% and genital dystrophy 60%. The familial incidence of the syndrome was 48%. However, this figure should be higher if the isolated characteristics segregating in the pedigrees are also taken into account. Undoubtedly, the populational frequency of this syndrome is extremely

low, and the affected individuals generally come from isolated communities where the rate of cousin marriages reaches high levels. The parents of the affected subjects are apparently normal and show a high frequency of consanguinity. These facts suggest that this syndrome follows a recessive pattern of inheritance. However, *Macklin* (1935) found that the frequency of affected among siblings of the propositi was higher ($28.5 \pm 1.9\%$) than the expected value but not significant at a 5% level of probability. Similarly, the excess of affected males ($58.7 \pm 6.1\%$) was not significant (*Burn*, 1950) and the fact that the male cases are more easily diagnosed might be responsible for this excess. The hereditary pattern of the pedigrees could be explained by the presence of a pair of recessive genes with pleiotropic effects evidenced by different symptoms. The large variation in expressivity of this pair of genes has lead some authors to postulate the possibility of two or more linked gene pairs. A chromosomal aberration that could account for this syndrome has not yet been observed (*Harnden*, in anonymous Lancet editorial, 1959). The purpose of this paper is to report a pedigree of L.M. syndrome with uncommon features.

Case report

M.I.d.S., a 12 year old white girl (fig. 1), was first seen at the outpatient clinic of the Hospital das Clinicas, in November, 1959. According to her mother, the patient had been putting on weight since she was 6 months old. A full term baby with normal delivery, she was not obese at birth. She started to walk when she was one year and three months old and talked at 5 years of age. At seven, pubic and axillary hair began to appear; simultaneously, hair also appeared on the legs and arms. By the time she was 10, the hair had increased and reached the abdomen and the intermammary region; at that time the patient showed some hair on her face, too. She was nine when she had her first menstruation of four days' duration. Menstrual cycles of thirty days reportedly occurred regularly for 4 months; then the menses were interrupted spontaneously and she has remained amenorrheic since then. Her mother complains of impaired hearing in the girl, more accentuated on the right side. At school, she remained for three years in the first course, not even learning to read.

On physical examination, temperature and respirations were within normal limits. The pulse was 82/min. Blood pressure 140/85 mm Hg. Weight 82.00 kg. Height 155.5 cm. She was very slow in answering questions, and it was impossible for her to give plausible answers to the *Ishihara* (1957) test for daltonism. Pupillary reactions were normal. On fundoscopic examination, the papilla of the left eye showed a cloudiness on its temporal inferior edge and its inferior pole. The retina and vessels had no alterations, pigmentation was not present. The campimetric examination was prejudiced by the mental deficiency of the patient.

An ancient sequela of a cicatrized otitis media was present and the impaired hearing was explained by the perforated tympanus. Radiological studies revealed a chronic bilateral

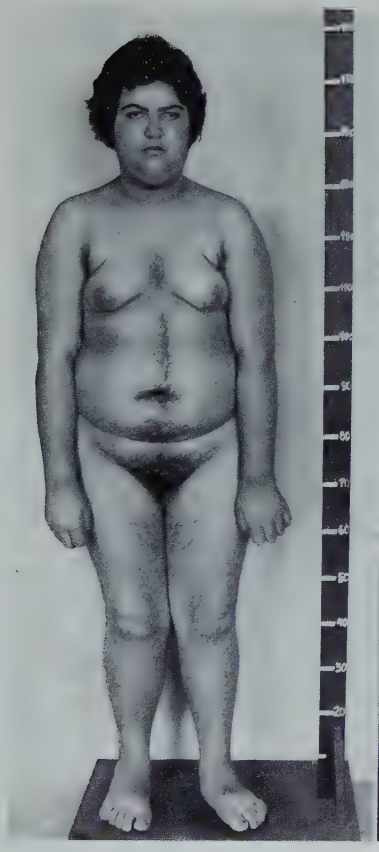

Fig. 1
A. M.I.d. S., 12 years of age, the propositus.

Fig. 1
B. Close up of the propositus.

otomastoiditis with a suspected cholesteatoma. Surgery was attempted but there was an unusual bleeding that puzzled the surgeon who thought the patient had a special contexture of the bones. An audiogram revealed a practically normal bone conduction, air conduction had a 2.8% reduction on the left and 22.6% reduction on the right side. The patient had polydactyly on both feet (fig. 2). The external genitalia (fig. 3) were somewhat prepubertal. A laparoscopy identified a reduced uterus with very thin Fallopian tubes. The left ovary was big, pale white and its surface was full of subepithelial follicular microcysts. A laparoscopical biopsy was made and an extreme reduction of the primordial follicles in the majority of the fields (fig. 4) was observed. No mature follicle was seen. An extensive area of collagenous tissue involved the subcapsular area mixing with the conjunctive elements of ovarian stroma.

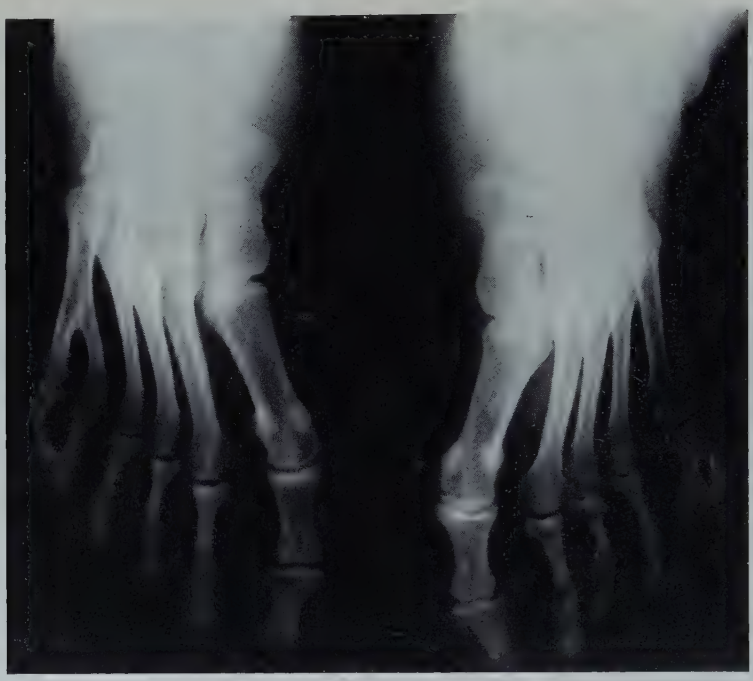

Fig. 2

Radiograph of the feet of the propositus, showing polydactyly on both.

Laboratory findings: Anthropological measurements gave the following results: Head length: 186 mm. Head width: 150 mm. Bizygomatic distance: 112 mm. Nasal width: 25 mm. Arm lenght: 526 mm. Leg lenght (pubis malleolus 526 mm), hand lenght: 179 mm. Thorax lenght: 516 mm. Thoracic perimeter: 890 mm. Thorax anteroposterior diameter: 176 mm. Transversal toracic: 248 mm. Abdominal anteroposterior: 171 mm. Abdominal transverse distance: 246 mm. Thyroidal radioiodine uptake was within normal limits. PBI was normal (6.7 mcg/100 ml serum). The urinary output of gonadotropins (*Bradbury et al.*, 1949) was 16.5 mouse units per twenty-four hours. X-ray examination showed a normal sella and there was no hyperostosis of the inner table of the frontal bone. The bone age was 17 years, the urinary excretion of 17-ketosteroids (*Drekter et al.*, 1952) was 17.98 mg per 24 hours and of 17-hydroxycorticoids (*Butt et al.*, 1957) 9.86 mg per 24 hours. An intravenous ACTH test performed over a period of eight hours for three successive days showed a decrease of the eosinophils by 98% in the first day. The 24 hour output of 17-ketosteroids increased from 14.8 to 26.7 mg on the first and 32.6 mg on the second day, falling to 21.5 on the third day. The 17-hydroxycorticoids increased from 9.86 mg on the first day to 48.8 on the second day, falling to 33.2 mg on the third day, revealing a probable hyperactivity of the reticular zone of the adrenals. The basal metabolic rate was +22 +19% (Jones pattern.)

Fig. 3

External genitalia of the propositus.

The serum proteins, cholesterol, lipoproteins and fasting blood sugar were within normal values.

In oral smears 40% of the cells were chromatinpositive. In blood smears the characteristic drumstick was present in 7 out of 250 segmented neutrophils counted.

The blood types were the following A1/B/MN/CcDE(Rh1Rh2)/Fy(a+)Kell–

The blood types of the parents were the following:

Mother: A1/MN/Rh1Rh2(CcDE)/Kell–/Fy(a+)

Father: B/MN/Rh1Rh1(CCDee)/Kell–/Fy(a+)

The finding of obesity, hypogenitalism, mental retardation and polydactyly made us consider this case as a probable case of L.M. syndrome, although retinal pigmentation was lacking and the patient showed hirsutism with a rather high excretion of the 17-ketosteroids in the urine.

Family history

Family data were obtained separately from both of the parents. The information taken from each parent of the propositus was compared and the

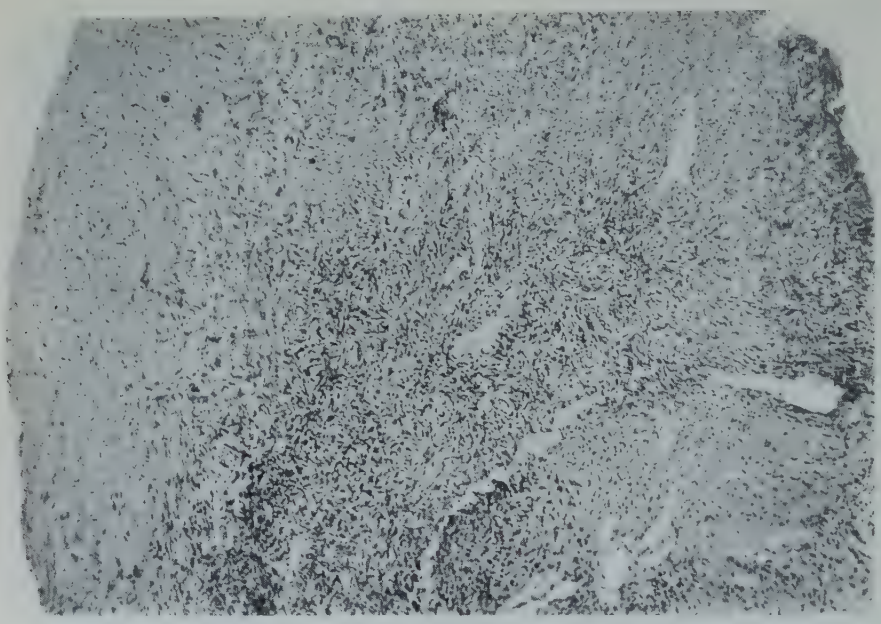

Fig. 4

Ovary of the patient, laparoscopic biopsy. The cortex is thick. No mature follicles are seen.

pedigree elaborated (fig. 5). The parents of the patient and her three siblings did not show any of the symptoms of the disease. These symptoms were not observed in members belonging to the first two generations but this situation might be due to the insufficient information obtained from the parents of the propositus. One of the most interesting features of the pedigree is the presence of isolated symptoms of the L.M. syndrome segregating in the generation of the propositus and the earlier one. In generation IV, various members suspected of having symptoms of the disease were carefully examined and four individuals (n° 14, 16, 17 and 18) were found to be affected with typical retinitis pigmentosa. The fundoscopic examination of the case numbered 17 revealed that both eyes presented slightly pale papillae of normal form, level and dimensions. The macular region of both eyes was occupied by rough pigmented alterations forming alveolar figures across which choroidea and its vessels could be observed. This pigmented area had approximately two papillary diameters. Clumps of pigment with irregular distribution, different shapes and dimensions, sometimes osteo-

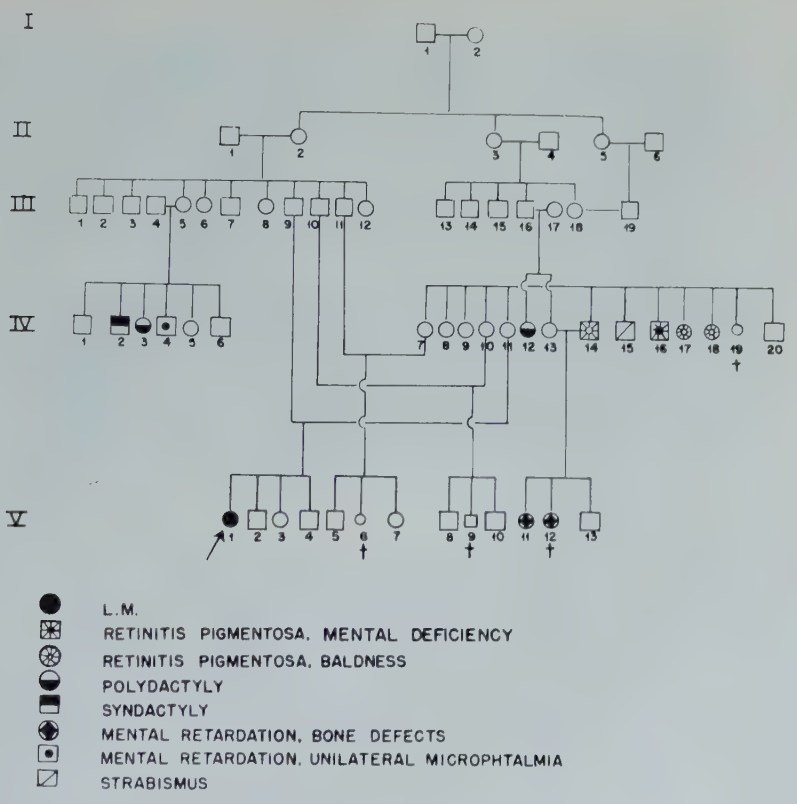

Fig. 5 Pedigree of the L.M. family.

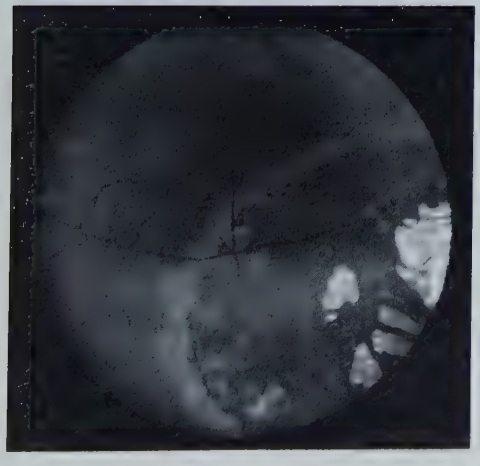

Fig. 6

The fundus of individual No. 16, showing rough retinal pigmentary degeneration.

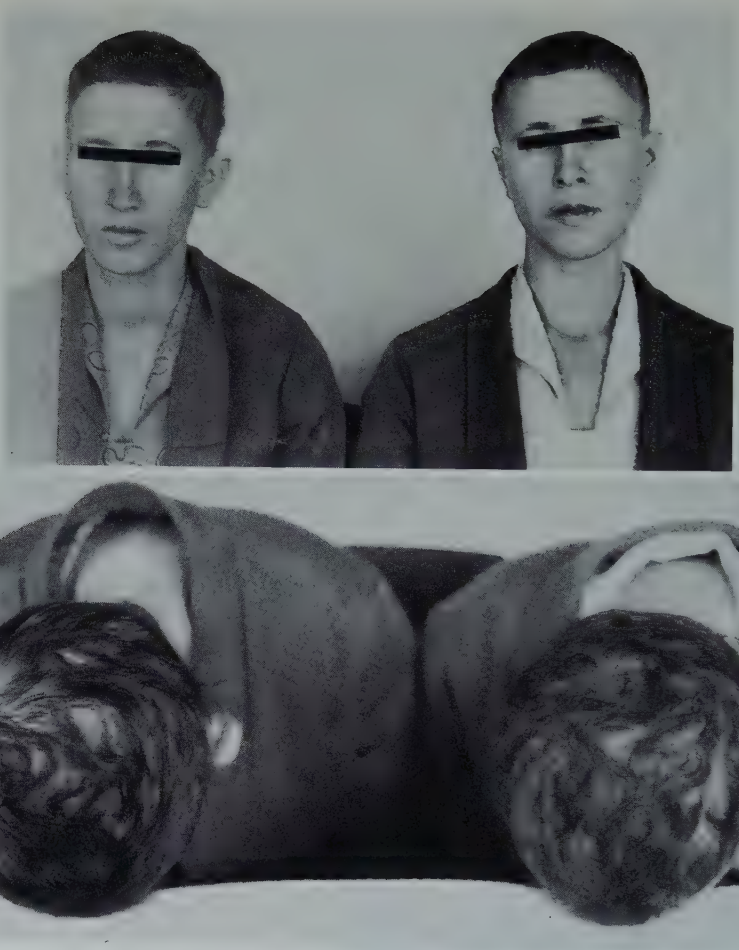

Fig. 7 and 8
Baldness in two maternal aunts of the propositus.

clastlike, were observed to invade the whole posterior pole which had a nacreous appearance. Narrowed arteries with a broad central reflex were seen. Veins were within the limits of normality. The retinal alterations were somewhat similar on the four individuals. The retina of the individual numbered 16 is seen on figure 6. Three of the individuals presenting retinitis pigmentosa also exhibited baldness (fig. 7 and 8). The individual numbered

16 had mental subnormality and no hair until recently, when sparse hair appeared on his scalp. The individual numbered 12 had polydactyly.

Polydactyly, syndactyly, mental debility and microphtalmia were found in another sibship belonging to the same generation (n° 3, 2 and 4). In the generation of the propositus, two cases of mental retardation associated with bone defects were present. Excepting the individuals with polydactyly (n° 3), syndactyly (n° 2) and mental deficiency (n° 4), whose parents do not seem to be related, all the affected members had related parents. There are several cases of multiple relationship among the parents of the affected individuals: the individuals numbered 18 and 19 of generation III were first cousins (f=1/16). The individuals numbered 13 and 14 generation IV showed multiple consanguinity (f=5/64). There were three marriages between members belonging to the third and fourth generations, including the parents of the propositus (f=1/16), these being first cousins once removed with multiple consanguinity.

Discussion

Data hitherto collected indicate that the L.M. syndrome follows an autosomal recessive pattern of inheritance. However, the exact genetical determination of the disease is still far from being completely understood. Since this syndrome is a rare one, the affected individuals should have normal parents and are mainly from isolated communities where high levels of cousin marriages occur. The present case comes from a geographical isolate in the inner part of Brazil (Pouso Alegre, Minas Gerais) where the total frequency of consanguineous marriages reaches an average of 6.62 per cent (*Freire-Maia*, 1957). As can be seen in figure 5, the parents of the propositus are related and apparently normal. The proportion of affected individuals in the sibship of the propositus agrees with the expected values in the basis of simple autosomal recessive inheritance. However, the propositus is not a complete case of L.M. syndrome. The fundoscopic examination reveals only a cloudiness of the left papilla with no sign of retinal pigmentation. Since retinitis pigmentosa as an isolated symptom is found in several members of the previous generation (on the maternal side), it is possible that this symptom could later appear in the patient. Furthermore, the presence of typical retinitis pigmentosa in four subjects in the same

pedigree could hardly be taken as an independent event. Isolated retinitis pigmentosa is found among children of consanguineous parents, agreeing with the fact that the trait has been most commonly described as a simple recessive one. Other symptoms of the L.M. syndrome, all recessive with the exception of the most commonly dominant polydactyly-syndactyly complex occurred isolatedly in several individuals with closely related parents.

It is difficult to explain why the complete syndrome did not occur among other members of this pedigree, considering that a large part of the marriages were closely consanguineous and the syndrome is determined by simple recessive genes in homozygosis. To explain the present pedigree by simple recessiveness, it should be postulated that the gene responsible for the L.M. syndrome shows an unusual pattern of pleiotropy and an uncommon variation of expressivity. The fact that gene effects involve alterations of tissues of both ectodermal and mesodermal origin and the isolated occurrence of the different symptoms should suggest multiple genic determination.

Since the polydactyly-syndactyly complex is commonly determined by an autosomal dominant gene, one could imagine that this gene should interact with another recessive one, as, for instance, the gene causing retinitis pigmentosa and mental deficiency (*Hallgren*, 1959), to produce the complete syndrome. The location of the two or more gene loci, whether on the same or different chromosomes, is not important, because when the population reaches genetical equilibrium, the frequency of the syndrome shall be equal to the product of the frequencies of the isolated symptoms in the population. According to *Kemp* (1950) the frequency of retinitis pigmentosa in Denmark is about 1/10,000 and *Böök* (1951) stated that the rate of polydactyly in Sweden is about 1/1000.

Assuming that the L.M. syndrome is determined by the interaction of the polydactyly gene in heretozygosis and the retinitis pigmentosa gene in homozygosis, the frequency of the individuals with the complete syndrome should be about 1/10,000,000, not taking into account the consanguinity. However, there are no data on the frequency of L.M. syndrome in the general population to be compared to that figure. As we assume that the affected subjects are homozygous for the gene of retinitis pigmentosa we are to expect a high level of parental consanguinity, which is in fact what is found in the literature. Moreover, most of the individuals affected with L.M. syndrome should be the product of marriages with one parent heterozygous for both genes and the other parent homozygous for the normal

gene of polydactyly and heterozygous for the gene of retinitis pigmentosa (PpRr $\times$ ppRr).

The proportion of the affected children among siblings of the propositi should be 12.5% and sometimes one of the parents could be affected with polydactyly. Similarly this trait should be found among the siblings of the propositus, according to the penetrance of the polydactyly gene. *Blumel and Kniker* (1959) reviewed the literature since 1949 and showed that polydactyly is the most common symptom of L.M. syndrome occurring among the relatives of the propositi, mainly among their siblings. In fact, cases of L.M. syndrome with one of the parents affected with polydactyly have been described (*Wu*, 1956). However the proportion of affected individuals found among siblings of the propositi seems to be higher than the figure expected on the basis of the above hypothesis. An alternative genetical explanation for the L.M. syndrome should be the presence of a chromosomal mutation, as, for example, a deletion in anyone of the chromosomes which in homozygosis could determine the syndrome. It is difficult to imagine a visible chromosomic alteration such as an extremely small deletion as should be the case here.

Special consideration must be given to the presence of baldness simultaneously with retinitis pigmentosa in three members of the maternal side of the propositus (generation IV). Since two of the individuals affected with baldness are women and have closely related parents it is most probable that they are homozygous for the gene determining baldness. This fact agrees with the hypothesis of a sex-limited trait proposed by *Snyder and Yingling* (1936).

Summary

A pedigree of L.M. syndrome is reported. The propositus with normal and consanguineous parents had four of the characteristic symptoms of the disease, lacking only retinitis pigmentosa which was, however, present in four of her mother's sibs. Some characteristics of L.M. syndrome were found to segregate as isolated symptoms in related members of the pedigree. Congenital baldness in two daughters of first cousins occurred in the same family. The interaction of a gene pair in heterozygosis and another in homozygosis is admitted as the possible determinant cause of disease. The existence of a small deletion difficult to identify in chromosome studies is suggested.

Zusammenfassung

Es wird über einen Stammbaum von L.M.-Syndrom berichtet. Der Propositus, dessen Eltern normal und blutsverwandt waren, hatte vier der charakteristischen Symptome der Krankheit, nur Retinitis pigmentosa fehlte, die jedoch bei vier Geschwistern der Mutter vorhanden war. Einige Kennzeichen des L.M.-Syndroms erschienen als isolierte Symptome bei mehreren unter sich verwandten Mitgliedern des Stammbaums. In der Familie fand sich ferner Kahlköpfigkeit bei zwei Schwestern, deren Eltern Vetter und Cousine waren. Als mögliche Ursache der Krankheit wird Wechselwirkung eines Genpaars in Heterozygotie und eines anderen in Homozygotie angenommen. Vermutlich besteht eine engbegrenzte, in Chromosomenstudien schwer nachweisbare Zerstörung («deletion»).

Résumé

L'arbre généalogique d'une famille présentant un cas de syndrome de L.M. est exposé. Le proband issu de parents normaux et consanguins accuse quatre des symptômes caractéristiques de la maladie. La rétinite pigmentaire est absente chez lui mais elle a été observée sur quatre de ses tantes et oncles maternels. Plusieurs membres de cette famille présentent isolés, quelques-uns des traits propres au syndrome de L.M. Deux sœurs, de la même famille, filles de cousins germains sont atteintes d'alopécie congénitale. L'interaction d'une paire de gènes en hétérozygose et d'une autre en homozygose est admise comme l'une des possibles causes déterminantes de l'entité clinique. L'existence d'une petite délétion difficilement identifiable par les études chromosomiques est suggérée.

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Authors' Adresses: Dr. Nelson Leon, A. da Silva Coelho Neto and Prof. A. B. de Ulhôa Cintra, Department of Endocrinology of the First Medical Clinic, Hospital das Clinicas, *São Paulo* (Brazil), Dr. Celso A. de Carvalho, Department of Ophthalmology, Hospital das Clinicas, *São Paulo* (Brazil), Dr. P. H. Saldanha, Laboratório de Genética Humana, Faculdade de Medicina, Universidade de São Paulo, Caixa Postal, nº 2921, *São Paulo* (Brazil).

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From the Department of Anthropology, Museum of Natural History, Budapest, Hungary

IVÁD: AN ISOLATE IN HUNGARY

By J. NEMESKÉRI and A. THOMA

Introduction

Studies of small human isolates do not mean searching for curiosities. Studies of this kind may contribute valuable information to the increasing knowledge of human population genetics, a science moving more and more from the purely theoretical toward the empirical phase. Thereby we have summed up the aim of the present paper, adding that our material originates from a «terra incognita» from this respect, from Hungary.

One of us, J.N., who had been studying the physical anthropology of the living population of Hungary, strove to base the racial history and structure upon an exploration of the genealogical roots of the populations. Searching for material suitable for such a kind of model study he discovered in 1939 a community in Northern Hungary, 2/3 of its population belonging to one large family.

The community (village) is called Ivád (in the county Heves) and the name of the family is Ivády. J.N. carried out the genealogical and physical anthropological studies of the population un question in the period from 1940 to 1942. The first report was published in Hungarian (*Nemeskéri*, 1944). After World War II, the work was continued and extended, with the help of historians, sociological, demographic and medical experts (historian Dr. *A. Csizmadia;* sociographic, demographic and ethnographic expert Dr. *Gy. Acsádi;* pediatrist Dr. *Gy. Ivády*, a member of the family; medical expert Dr. *E. Wallner;* hygienic expert Dr. *V. Molnár;* gynecologist Dr. *Gy. Neubauer;* somatologist Dr. *D. Hattyassy;* serologic and immunologic expert Dr. *R. Backhausz;* studies on phonetics and musical memory by Dr. *T. Tarnóczy*). A detailed informative monograph without the medical evidence was published in Hungarian later (*Acsádi, Nemeskéri et al.* 1953). Owing to financial and other difficulties the medical exploration could not be continued and the conclusions in 1952 cannot be considered to be final.

It is impossible to deal with the innumerable aspects of human population biology. For this reason also this report has a restricted aim. Here we publish only the genetical demographic results and those relating to variation analysis.

The history of the isolate

The community is located in Northern Hungary, at the Northern margin of the Mátra mountains, in the hilly country of the Gömöri basin, in county Heves. On three sides the village is surrounded by low mountains, 340 to 370 m. high. The geographical gateway of Ivád lies in the direction of a rivulet running East, toward Pétervására. The geographical isolation of the village is due not so much to the presence of mountains as to the separating effect of the enormous woods which existed here.

The community was first mentioned in the 15th century by the name of «Iwagh». The first data concerning the family constituting the isolate originate from 1617, from the will of Imre Ivády, who had been born in the 16th century. The family was ennobled in 1656, when the brothers György, János and Gergely Ivády and their children were raised to the nobility by Emperor Ferdinand II. The Ivádys of today originate from these three ancestors. According to documents, the Ivádys of that time were living at Pétervására and the locality Ivád was merely a range. In 1738 the family moved there for economic reasons. Subsequently, the Ivádys of that time married extraneous persons. The first sign of isolation is the first Ivády-Ivády marriage which took place in 1759. From that date on the Ivádys began to marry Ivádys, but late in the 18th century this did not amount to even 10 per cent of all marriages in the family. It was in the third decade of the 19th century that the Ivády-Ivády marriages began to reach increasing proportions, with 30 to 50 per cent of the total number of marriages taking place within the members of the family. Also, in that period patrilinear separation began to take shape. The period 1840–1900 was the most decisive from the point of view of the development of the isolate, mating within the «great family» having then become common practice.

Separation to lineages also took place at that time. Within the «great family Ivády» 21 lineages developed, which had surnames still known today. Already in the 19th century two of the lineages died out on the male side and now 19 can be distinguished among the Ivádys living today.

At the time of separation into lineages there was community of land in the family. After the separation became complete, the community of land was dissolved and this had a decisive influence on the development of the isolate. Early in the 18th century, when the Ivádys moved to the range, the arable land of the Ivád range measured about 680 acres, owned in its major part by 12 adult males of the family and in a minor part by extraneous owners. As a result of the separation into lineages and of the increase in the number of the members of the great family, the land area could only be enlarged by deforestation and after the community of land broke up fragmentation of the land could be prevented by endogamic marriages only. Late in the 18th and early in the 19th century the lands owned by the single lineages were similar in size (about 30 acres).

In the 1840-ies one of the lineages (*Hegyi*), separated by favourable exogamous marriages, at the expense of the great family, increased its property fivefold, then in the 20th century tenfold including considerable forest areas. This increase in the size of the land owned was due, beside the possibilties given by the financial situation, to the fact that the

lineage *Hegyi*, once closely related to the Ivádys but not longer caring about it, arranged the commassation of land at the expense of the other lineages. As a result, the social strata within the great family underwent a considerable shifting; the proportion of medium landowners decreased and the small farmers increased in number. The latter tried to secure economic survival and relied even more upon endogamic marriages. The economical factors mentioned led, on the one hand, to a social differentiation and on the other, to the fact that the number of Ivády-Ivády marriages reached a peak during the second half of the 19th century. It should be mentioned among the historical and economic factors involved that, as a result of geographical isolation, the members of the family could earn a living exclusively by farming or cattle raising within the biological district of the community and thus mating was restricted by a lack of choice in the community which was distant from the main lines of communication anyway.

There were two noteworthy epidemics in the history of the isolate, one in 1831 and the other in 1873. In both of them $^1/_4$ of the population was killed by cholera. As a result, the choice in mating was even more restricted and it was also near this period that the commassation of land took place. Most of the ecclesiastic dispensations were issued during that period and also the frequent cases of sororates and levirates should be mentioned here. The losses caused by the epidemics can be clearly appreciated if we realize that the total number of killed later in wars (War of Liberation 1848–1849, World War I and II) was but a fraction of that lost in those outbreaks. Except for the lineage *Hegyi*, the rest of the family remained greatly family-conscious. This is illustrated also by the fact that all of the 12 adult men of the Ivádys who went to try their luck in America early in the 20th century returned home within 5 to 6 years, as recorded in the family chronicles.

During the first decades of the 20th century, and especially after World War I, the isolate stood united and was even reinforced by the marriages of the men who had returned from the war. The rapid industrialisation following World War II decisively altered the

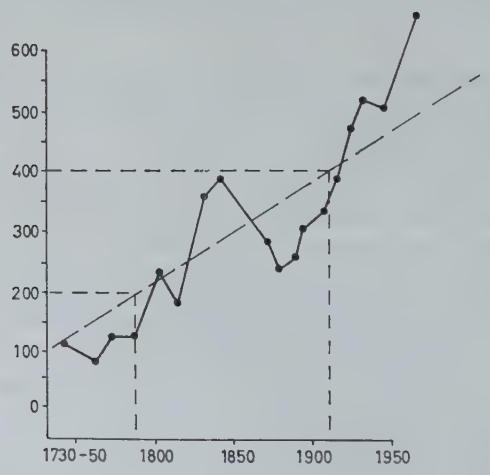

Fig. 1
Growth of the Ivád population. Ordinata: population estimated ad different periods, from various sources. Abscissa: time.

fate of the isolate. The boundaries of the isolate were broken up by the new means of communication, the newly founded industrial plants and mines and the population of Ivád swarmed out to find jobs in the factories, workshops and mines of distant areas. As a result, they had a better and wider choice in mating and in our days the isolate is seen to be breaking up completely. This fact is proved best by the following data: in the 18th century there had been a few marriages with people living 4 to 5 km. distant, in the 19th century 4 or 5 in a decade married persons living 8 to 10 km away, while in the past 20 years marriage with persons living far away followed by departure from the village has become a commonplace event.

Finally, we should mention a few data important from the point of view of the order of magnitude of the isolate. The increase in the number of the population in the isolate during the 18th century may be reconstructed on the basis of legal documents, urbarial and ecclesiastic registered data (Fig. 1). The archival records of 1753 mention 8 families, a total population of about 40. By the end of the 18th century this number increases to about 300, then early in the 19th century the data from the conscription ordered in connection with the mobilisation of the nobles against Napoleon suggest that the population totalled 265 persons, including 20 Ivády families with 56 adult men. From the second half of the past century we have the data obtained by census. As a result of the epidemics mentioned, the number of the population decrease from the 316 persons in 1869 to 266 by 1880 and to 293 by 1890. Around the turn of the century and later, the number increases again from 338 to 428 and in 1949 those living in the village number 561. The latter constitute 90 families, of which 72 belonged at the time of study through the male line to the great family of the Ivád isolate. The 18 foreign families also had connections (through the female line) with the isolate. According to the preliminary data of the 1960 census the population numbered 661 persons.

On the basis of the records, family or official, dating back 250 to 300 years, the data for 5.200 individuals belonging to the Ivády clan could be detected and fitted into the family tree.

This served as the basis for further evaluation.

Inbreeding

The first task was to measure the degree of endogamy prevailing in the population. To facilitate evaluation, in column 1 of *Table I* we present the number of marriages between members of the Ivády family in percentage of the total number of marriages in Ivád, in periods of 50 years. As can be seen, the initial lower values are followed during the 19th century by a sharp rise; the ever-increasing tendency to endogamy culminates in the 20th century.

Realizing that the marriage records may greatly vary in accuracy and reliability, we selected the period 1866–1916, as one in which trustworthy data could be obtained from the records of the Roman Catholic Church. These data supply evidence as to the measure of consanguinity of the parents and grandparents of the adult population studied around 1940. It

Table I

Changes in endogamy and infant mortality rate in Ivád

Period	Ivády M × Ivády F marriages in percentage of the total number of marriages	Number of deaths at 0 to 1 year, in percentage of the total number of deaths	0 to 1 year deaths, in percentage of total number of live births
1751–1800	3.5	24.9	16.9[1]
1801–1850	18.0	26.0	21.5
1851–1900	30.2	30.6	25.8
1901–1940	36.3	38.7	23.5

[1] 1771–1800

was essential to make the following restriction. Since the commassation of land in 1872 several farm hands had come to the Ivád isolate and their marriages were entered in the same registers. Not a single marriage took place between these heterogeneous, migrant elements and the small-holder Ivádys or the members of families other than Ivády living there for a longer time. This portion of the population falling outside the borders of the isolate is not included in the evaluation. The 9 per cent of consanguineous marriages computed from the data in *Table II* represents a relatively considerable percentage. According to *Sutter and Tabah* (1948) 1.76 per cent of all marriages took place between consanguineous partners in France in the period 1926–1945, as determined from the records for dispensation. In the period 1926–1930 in Corsica and Savoy, the most endogamous areas, 8.2 and 11 per cent, respectively, was the frequency of consanguineous marriages, and these values decreased by about 50 per cent during the next

Table II

Consanguineous marriages in Ivád, among a total of 157 marriages, 1866 – 1916

Marriage between	Half siblings	First cousins	First cousins once removed	Second cousins	Third cousins	Total of consanguineous marriages
Number	1	5	3	2	3	14
Per cent	0.6	3.2	1.9	1.3	1.9	8.9

15 years. The data for Germany published by *Verschuer* (1954) show a 1 per cent frequency during the first half of the 20th century. The maximum values for the single parishes are: 4.19 per cent for the Archdiocese of Cologne and 8.4 per cent for the Oldenburg part of the Diocese of Münster. At present no data for comparison are available from Hungary.

No marriage of 2/1 degree had taken place in Ivád, in agreement with the observations made in the Osnabrück Diocese, where only 1 such marriage out of nearly 20 000 took place. In general, such marriages are less common than excepted, obviously because of the difference in age. The two third degree marriages represent a mere 14 per cent of all the consanguineous marriages, in contrast to the data for Germany, where marriages between second cousins make up everywhere more than the half of the consanguineous marriage total. Recent evidence tends to indicate that some of the marriages between more distant blood relations fail to take place. One of the reasons why this is so may be that the probability of departure increases with the distance from the common ancestor. However in the case of a given closed population we feel justified in assuming that in some instances of second cousin marriages no dispensation had been asked for. In one case maternal half siblings got married, by misleading the authorities. This marriage was annulled one year later, no child had come from it, and therefore this case was not included in computing the inbreeding coefficient.

The mean coefficient of inbreeding computed on the basis of consanguineous marriages of varying degree, which shows the probability of one randomly chosen individual to have the same two homologous autosomal loci is $a = 0.0028343$. This value is at any rate a minimum estimation. The value of alpha is usually only minimally increased by marriages between more removed relatives, but in the Ivád population characterized by a consequent tendency of marriage between such relatives this increase might be appreciable. It is also likely that marriage between third degree relatives was more common. In the case of random mating the probability of marriage between second cousins is expressed by the formula $c'' = 4\,(b-1)\,b^2/n$ (the values for the individual parameters see below). In this case the value of $c'' = 14.6$ per cent, in contrast with the 1.3 per cent value found.

The populations in *Table III* may be, rather arbitrarily, divided into three groups from the point of view of inbreeding. Under 10×10^{-4} are to be found the civilized areas in Europe and America, which are densely populated and possess well developed systems of communication. Presumably

Table III

Comparison of the mean coefficients of inbreeding of different human populations. Some data from *Böök* (1956)+ and from *Sutter and Tabah* (1948)++

Population (author)	Period	$10^4\alpha$
Germany, Archdiocese of Cologne (*Panse and Krings*, 1949)+	1898–1943	> 1
Brazil, Conceiçao da Feira (*Freire-Maia*, 1954)	1939–1949	> 2
France (minimum) Lot et Garonne (*Tabah and Sutter*, 1950)	1926–1945	> 2
Germany, Diocese of Münster (*Müller*, 1953)+	1944–1951	> 2
Germany, Diocese of Osnabrück (*Hoge*, 1952)+	1946–1950	> 3
USA, State of Utah (*Woolf* et al., 1956)	1890–1909	> 3
Austria, Archdiocese of Vienna (*Orel*, 1932)+	1901–1930	> 6
Sweden, parish of Pajala (*Böök*, 1956)	1890–1946	> 8
Sudan, Tir, Dinka village (*Roberts*, 1956)	1954	> 15
France, (maximum), Corsica (*Tabah and Sutter*, 1950)	1926–1945	> 23
Sweden, parish of Junosuando (*Böök*, 1956)	1890–1946	> 24
Yugoslavia, island of Susak (*Dolinar*, 1960)	1953	> 26
Hungary, Ivád (present study)	1866–1916	> 28
Japan, Hiroshima (*Neel* et al., 1949)	1948–1949	> 29
Japan, Nagasaki (*Neel* et al., 1949)	1948–1949	> 39
USA, Bunkerville, Mormon descendants (*Woolf* et al., 1956)	1930–1950	> 43
Germany, Protestant isolate on the Rhine (*Nöllenburg*, 1932)++	1840–1889	> 50
Sweden, parish of Muonionalusta (*Böök*, 1956)	1890–1946	> 58
USA, Ramah Navaho Indians (*Spuhler and Kluckhohn*, 1953)+	1920–1948	> 66
India, Maratha caste (*Sanghvi*, 1954)+	1950	> 74
Germany, Hohenzollern, Jewish isolate (*Reutlinger*, 1922)+	1875–1920	> 110
Brazil, Indaiá de Itapecerica (*Freire-Maia*, 1954)	1951	> 118
Brazil (maximum) S. Seb. do Curral (*Freire-Maia*, 1954)	1951	> 137
USA, Dunker religious isolate (*Glass* et al., 1952)	1895–1931	> 254

(and only presumably, as data from China are not available) the majority of 20th century humanity is characterized by the system of exogamous marriage. The limits of group 2 may be drawn at 20 to 60 $\times 10^{-4}$. With these populations special factors (geographical or social isolation) cause a significant increase in the degree of inbreeding. Over them can be found the populations characterized by extreme endogamy: the Amerindians living in reservations, Indian castes, small communities living distant from one another in Inner Brazil, religious sects. Ivád belongs to the second group and is undoubtedly endogamous as far as European relations are concerned.

The size of the isolate was at first estimated by applying *Dahlberg's* formula (1943), starting out from the frequency of marriages between first cousins. In the given case c = 0.0318. From *Fig. 1.* it is clear that the population of Ivád was doubled in about 5 generations, thus the number of siblings reaching reproductive age averages; b $\approx$ 2.3. On the basis of these parameters the size of the isolate is n = 188. To control these results, the estimation was also made directly. In the given period the age of the fathers at the birth of the children averaged 34.7 years, that of the mothers 28.3 years, thus the mean duration of a generation was 31.5 years. Thus, the 314 persons got married over a period of 1.6 generations. From that the size of the isolate is estimated at n = 196. The good agreement with the results obtained by the two methods shows clearly that from the point of view of mating the Ivád population is of homogenous structure: it is not divided into sub-isolates. The value obtained is definitely low: matings were restricted to a narrow circle. In the Europe of older times *Dahlberg* (1943) estimated the mean size of isolates at 400 persons, as compared with the value of 1600 for recent periods. *Sutter and Tabah* (1955) found the following mean values of isolate size for two French départements: Loire-et-Cher 1919–1925: 270 individuals, 1944–1945 810 persons; Finistère, in about the same two periods, 1061 and 2122, respectively.

From the point of view of further evaluation it is of extreme importance to determine whether the random genetic drift may take effect in the population characterized by the given parameters. According to *Sewall Wright* (cit. by *Roberts*, 1956) in the case of an initial gene frequency of q = 0.5 there may still be a drift-caused differentiation, if the product of effective population size (N_e) and migration rate (m) is smaller than 50. We have estimated this value indirectly, by a simple formula derived from the equation of *Sewall Wright* (in *Glass et al.* 1952, p. 150):

$$N_e m = \left(\frac{1}{\alpha} - 1\right) \frac{1}{4} = 89.$$

Thus, it is unlikely that the genetic drift would affect the Ivád population, or at the least it might alter the allele frequencies in a negligible measure only.

Blood groups

To control the occurrence of drift the blood groups are the most sensitive markers. In their sero-anthropological studies extending to Hungary as a whole *Backhausz and Nemeskéri* (1960) also present data for Ivád and its

neighbourhood, which we take over from their work. In that area the data were collected in 1948. We select two series for comparison: the Eger samples (Eger is a town 30 km from Ivád, having a population at the time of sampling of about 30,000), and the «neighbourhood» samples, including individuals living in the villages around Ivád and Eger.

The frequencies observed and those expected of the ABO-system do not differ significantly from one another in either of the series, thus the populations are in the state of panmixia, and there is no reason to doubt the reliability of the determinations. Phenotypic distribution and gene frequencies are shown below.

	No.	O	A	B	AB	r	p	q
Ivád	23	150	241	86	46	0.5352	0.3286	0.1363
Eger	1160	370	492	194	104	0.5678	0.2990	0.1335
Neighbourhood	175	57	69	34	15	0.5715	0.2778	0.1506

Examining the phenotypic distribution of the three series in a 3×4 contingency table, no significant difference is found from the O-hypothesis of homogeneity ($\chi^2_{[6]} = 3.889$; $70 > P > 50$ per cent).

The investigators had only anti-D serum available for determining the Rh blood types. In the three series the phenotypic distribution and gene frequencies had the following values:

	No.	Rh+	Rh—	D	d
Ivád	523	437	86	0.5945	0.4055
Eger	1160	966	194	0.5901	0.4099
Neighbourhood	175	142	33	0.5657	0.4343

As can be seen, the gene frequencies stand very close to one another. The test in the contingency table for phenotypic distribution shows no significant difference between the three series: $\chi^2_{[2]} = 0.652$; $90 > P > 70$ per cent.

Thus, no Sewall Wright effect was observable in these two autosomal loci strongly exposed to random fluctuations. This observation confirms the theoretical conclusions drawn in the previous chapter.

Infant mortality and lethal factors

The medical studies mentioned in the Introduction and not yet completed have not brought to light special, hereditary defects. Some variations of denture were found, blue sclera occurred in 15 cases (associated

with fragility of bone in 1 of them), and there was one case of ichthyosis universalis congenita. Interesting results may be expected in a relatively much studied field, that of postnatal lethal factors.

It is hardly questionable that the lethal, semilethal and subvital factors are just as common to man as they are to domestic animals (*Hadorn*, 1955 whose terminology will be used in the following), but the notorious exogamy of humanity keeps the frequency of homozygotes at a low level. Deviation from this may be expected to occur in two situations, identical in their sequelae: (*Fraser Roberts*, 1959) in small breeding populations, in which the Sewall Wright effect is active, and with the offsprings from consanguineous marriages. The former is not merely a theoretical postulate any longer: there are now most valuable empirical investigations (*Birdsell*, 1950, *Glass et al.* 1952; *Böök*, 1956; *Dolinar*, 1960) proving the existence of extreme gene frequencies and increased homozygosity resulting from factual loss and fixation of alleles. As early as 1950, *Sutter and Tabah* stated that in the French population a high, positive correlation existed between the mean coefficients of inbreeding and the rates of perinatal mortality, proving that inbreeding had in fact an influence upon the accumulation of lethal factors. According to more recent evidence (*Böök*, 1957; *Sutter*, 1958; *Schull*, 1958; *Slatis et. al.*, 1958) the offsprings from consanguineous marriages (first of all from those between first cousins) did not differ from the controls as regards prenatal events, but the mortality rate of infants and children was definitely increased. The genetical basis and the mechanism still have many aspects to be clarified and it is here that the researches in Ivád may be fitted into the pattern of pertaining investigations.

The present studies are based upon the data of parish registers and are therefore subject to certain limitations. In the registers of births the name of both parents is shown. In the death registers both parents are mentioned by name if the deceased was an infant (a baby less than 1 year old at the time of death), in the periods 1814–17, 1829–37 and 1855–1940. *Tables IV and V* contain the pooled data for these periods. The data relating to children deceased at older ages are not suitable for evaluation. Let us now return to *Table I*, to make a start. In column two the number of dead infants is expressed as a percentage of the total number of deaths in the corresponding period. There is a conspicuous, continuous increase parallel with the increase of endogamy, that is in contrast with every experience. But the percentages thus computed agree only in the case of stationary populations with the correct rate of infant mortality, with the number of those not surviving 1 year among 100 live births. Here, too, the values in

column three are invariably lower than the corresponding ones in column two. Even so, there is a demonstrable increase in the first three periods, but it is followed by a minor decrease in the 20th century. As it becomes clear from the demographic study by *Acsádi* (in: *Nemeskéri et. al.*, 1953), the discrepancy is due to the fact that in the 20th century medical care produced a sudden improvement in the life expectancy of adults. The infant mortality rate, too, has been reduced, but in a much lesser degree. It is worth while to compare the data for Ivád with the infant mortality rates for Hungary as a whole. *Fáy* (1859) reported in the period 1837–1847 an infant mortality rate of about 23 per cent (as related to live births) as having occurred in smaller country communities. As to later periods, we take our data for comparison from *Rédei* (1960). In the period 1878–1880 infant mortality was still 25.4 per cent in Hungary. Thus far, Ivád did not differ from the rates for the whole country. However, in the 20th century there is some difference from the nation wide data, which are 22.3 per cent in 1900, 18.1 per cent in 1923–1925 and 13.4 per cent in 1940. On the basis of all these it may be substantiated in some measure (though it cannot, of course, be proved) that a causal relationship may exist between endogamy and infant mortality rate.

Continuing the analysis, we compare in *Table IV* the rates for those born from the different types of marriage. Those born from the endogamous Ivády marriages lead in the field of infant mortality rate. The children living at Ivád, but not born from Ivády parents, come closely after them. But this small difference in «genetic death» is made more significant by the fact that the peristasis of the «foreigners» (most of them hired farm-

Table IV

Number of infants not surviving 1 year, in percentage of all registered infants, according to types of marriage

Type of marriage	Non-survivors
Ivády with Ivády	25.7 ± 1.80
Ivády with non-Ivády	19.9 ± 1.48
Non-Ivádys	24.2 ± 2.16
Ivády M × non-Ivády F	23.4 ± 1.96
Non-Ivády M × Ivády F	13.7 ± 2.15

Table V

Sex ratio of the offsprings from the various types of marriage and of those not surviving 1 year

Type of marriage	Births			Non-survivors			
						Sex ratio	
	M	F	Sex ratio	M	F	rough	corrected
Ivády M × Ivády F	302	286	105.6	77	74	104.1	98.5
Ivády M × non-Ivády F	244	218	111.9	67	41	163.4	146.0
non-Ivády M × Ivády F	125	130	96.2	18	17	105.9	109.9
non-Ivády M × non-Ivády F	200	193	103.6	45	50	90.0	86.9

Tests of significance

Between all classes of marriage, for the sex distribution of newborns: $\chi^2_{[3]} = 0.215$; $P > 95$ per cent

For the sex distribution of non-survivors, between the offsprings from reciprocal marriages: $\chi^2_{[1]} = 12.339$; $P < 0.1$ per cent.

For survivor and non-survivor girls between the offsprings from reciprocal marriages: $\chi^2_{[1]} = 1.925$; $30 > P > 10$ per cent.

For survivor and non-survivor boys between the offsprings from reciprocal marriages $\chi^2_{[1]} = 7.950$; $1 > P > 0.1$ per cent.

Sum of the latter two: $\chi^2_{[2]} = 9.875$; $1 > P > 0.1$ per cent.

hands) is definitely inferior to that of the Ivádys. As compared with both extreme groups, the infants born from the exogamous Ivády marriages are the most viable. If we break up these offsprings into the two reciprocal classes, it will become clear immediately that the two groups differ sharply from one another as far as infant mortality rates are concerned. This phenomenon suggests the potential involvement of some sex-linked, lethal factors. The sex-linked factors are analysed in *Table V*. The variations in the sex ratio at birth are not significant; the suspected sex-linked lethals have no influence upon the prenatal events. In the crude sex ratio of the non-survivors the abnormally high value of the «Ivády male × non-Ivády female» class is conspicuous at a glance. The decisive proof is supplied by the infant mortality rates for the two reciprocal marriage classes. The difference between them in sex ratio is significant at the 0.1 per cent level. The difference is not much influenced if the sex ratio of the non-survivors is corrected according to the slightly different sex ratio at birth (last column). The pertaining tests indicate that the girls from reciprocal marriages do

not differ significantly in the distribution of survivors and non-survivors. The same test for the boys shows an excess mortality significant at the 1 per cent level for the «Ivády male × non-Ivády female» class and this excess alone is responsible for the 1 per cent level significant difference in the distribution of survivors and non-survivors even when the boys and girls are tested together. Taking into account all the possibilities, this phenomenon may be explained exclusively by the assumption that the exogamous marriages, through the carrier females introduce *sex-linked, recessive, lethal factors* into the Ivád population. This finding supports the view that besides the general weakness of the male sex the excess mortality of boys in certain populations is in fact due to the sex-linked recessive lethals. In the population from which these factors originate the sex ratio of the non-survivors should theoretically show a high value, too, although in the case of incomplete penetrance it might be somewhat lower than in the «Ivády male × non-Ivády female» class, because here the lethality is manifested not only in the hemizygous boys, but in the homozygous girls as well. The offsprings from the marriages between foreigners (non-Ivádys) living in Ivád do not realize this relationship. But this could be expected, because, as it has already been pointed out, the non-Ivádys living in the community do not represent the population from which the Ivádys marrying exogamously take their partners. The Ivádys tend to marry from an adjacent village (Pétervására). The origin and nature of the sex-linked lethals is subject to further research.

From what is outlined above, it follows that in judging the infant mortality rate of the «Ivády male × Ivády female» class it is exclusively the data for the «non-Ivády male × Ivády female» class that may furnish a realistic basis for comparison, as in the latter class the sex-linked lethals do not take effect. The test for the distribution of survivors and non-survivors between these two classes confirms at the 0.1 per cent level that endogamous marriages are associated with an increased infant mortality rate ($\chi^2_{[1]} = 14.842$). That the sex ratios of the two classes are trivial and do not differ significantly from one another, it eliminates the effect of sex-linked factors. It is absolutely unlikely that the phenomenon would be caused by a special, autosomal gene. As it has been mentioned, drift is unlikely. The mating structure of the Ivád population is homogenous, and thus it is not expected that a portion of the population on a given autosomal locus would show a distribution of alleles differing from the rest. An elimination of the offsprings of endogamous marriages from the population is artificial in this respect. However, when we put the question in reverse, it is

beyond doubt that the average degree of consanguinity is higher among the endogamous couples than among the rest. As to the total genotype, the offsprings of this group will be homozygotes on a greater portion of all the loci than the rest of the population although, of course, not always on the same loci. Thus, the only possible explanation for the reduced viability of the infants from endogamous marriages seems to be that the increased, but general, autosomal homozygozity acts as a unit, conditional, lethal-subvital factor that reduces the ability to resist peristatic noxae.

Table VI

Average number of children born in the various periods and from the various types of marriage

Period	I. Ivády M × Ivády F	II. Ivády M × non-Ivády F	III. non-Ivády M × Ivády F	t-values I–II	t-values I–III	t-values II–III
1750–1800	–	(50) 3.6±0.38	(12) 2.5±0.53	–	–	1.66
1801–1850	(46) 4.8±0.46	(92) 3.2±0.28	(15) 2.9±0.54	2.90	2.67	0.50
1851–1900	(57) 5.5±0.50	(49) 3.5±0.36	(24) 2.5±0.53	3.33	4.29	1.63
1901–1940	(61) 3.0±0.31	(48) 3.2±0.29	(39) 1.7±0.17	0.48	3.71	4.28

There is no need to attach detailed commentary to *Table VI*, showing the mean number of offsprings from the various types of marriage. Analysis of the data in the table will reveal that in spite of the periodic variations the differential fertility per class shows a compensatory behaviour as compared with the differential mortality due to the known causes. The mothers had tried to replace with new births the losses by death.

Twin births

Twinning tendency (at least in the case of dizygotics) is undoubtedly governed by hereditary factors (*Greulich*, 1946). In the period 1751–1940 the ratio of twinbirths to the total number of births was 45/2886, i.e. 1.559 per cent, a relatively high value. Crude data as to the actual twinning frequency in Hungary have been provided by *Kázsmér and Schleiffer* (1959), in part by personal communication. These data indicate a twinning frequency of 1.05 per cent for the period 1951–1957. (The total multiple

births amount to 1.06 per cent; no > 2 births have occurred in Ivád). To make this value suitable for comparison, two kinds of correction must be made. The probability of twinning is positively correlated with the age of the mother and parity, and these variables are also highly correlated with each other. In the period 1951–1957 the previous pregnancies of the mothers of the children born during that time averages 1.4, as compared with 2.8 for Ivád in the period studied. After the graphic equalisation made on the secondgrade regression curve plotted from the actual data the expectable frequency is found to be 1.34 per cent. However, it should also be borne in mind that the officially recorded twin births are exclusively those in which both twins are alive. At present this occurs with 9/10 of the twin births. Thus, the final, expected frequency is p = 1.21 per cent. With the given number of cases the standard error of the theoretical frequency is s_p = 0.203. The value of *t* is 1.719 – significant at the 10 per cent level with the two-sided and at the 5 per cent level with the one-sided test. In evaluation it should also be taken into account that under the less favourable conditions that had prevailed long ago the number of twin abortions must certainly have been higher. For example, *Fraccaro* (1956) found twinning frequency to have been 0.67 per cent in Pavia in the 16th and 17th centuries, as compared with the 1.39 value for 1955. As most of the twin births in Ivád took place during the 18th and 19th centuries the high frequency found is the more conspicuous. A certain measure of accumulation of the genes inducing twinning may have been responsible. Breaking up the material into two parts, it is found that with the members of the Ivády family the frequency is 1.075 per cent (the mean parity of this part of the population is 2.7), which is obviously not significantly different from the present value. Twinning frequency with the non-Ivádys living at Ivád is 25/1027 = 2.434 per cent, with a mean parity of 3. The difference from the theoretical frequency (1.24 $\pm$ 0.345) is significant at the 0.1 per cent level (t = 3.461). Thus, the high frequency of twinning found in Ivád is not a property of the Ivády family. It may be assumed that the twins from endogamous marriages fell victim more easily to abortion.

Variation of anthropometric characters

A population of similar breeding structure by itself suggests a most interesting problem: what measure of variation is shown by the quantitative, polygenic properties ? (In contrast with the rather inaccurate terminology used in anthropology, variation is understood to mean the observable

Table VII

Evaluation of the variances of 12 metric characters in the male population of Ivád. Explanation in text.

Characters	(n)	s^2	σ^2	χ^2	$\sqrt{2\chi^2} - \sqrt{2n-1}$	P (%)
Stature	(132)	27.04	33.64	105.60	-1.69 ± 1	< 5
Head length	(136)	33.64	38.44	119.68	-0.99 ± 1	≈ 16
Head breadth	(135)	23.04	27.04	114.75	-1.29 ± 1	< 10
Min. frontal breadth	(136)	22.09	24.01	125.92	-0.59 ± 1	≈ 28
Total face height	(137)	46.24	40.96	154.81	1.07 ± 1	≈ 14
Bizygomatic breadth	(135)	20.25	28.09	97.20	-2.49 ± 1	< 1
Bigonial breadth	(137)	44.89	33.64	182.21	2.57 ± 1	< 1
Nasal breadth	(136)	3.24	8.41	53.04	-6.17 ± 1	$\ll 0.1$
Nasal height	(137)	20.25	14.44	191.80	3.06 ± 1	≈ 0.1
Cephalic index	(115)	9.61	11.56	95.45	-1.32 ± 1	< 10
Total face index	(115)	29.16	26.01	128.80	0.92 ± 1	≈ 18
Nasal index	(115)	50.41	60.84	95.45	-1.32 ± 1	< 10
Total	(1566)			1464.71	-1.84 ± 1	< 5

phenotypic dispersion, as opposed to the theoretical concepts of genetical variability and peristatic adaptability).

The problem is analysed in *Table VII*, in the case of 12 anthropometric characters taken by the standard technique for the Ivády males. Column 1 contains the variances (s^2) of the sample with the corresponding degrees of freedom (n). These figures alone do not disclose much. For more precise evaluation, we compare the variances obtained with the squares of the mean sigma of *Howells* (1936) (σ^2). This latter has been obtained by the unweighted averaging of the standard deviations of more than 50 extensive series and may be considered to be the parameter of the mean human variation. Comparing row by row the observed and expected variances it will be found that in 8 out of 12 cases the corresponding parameter of the Ivády males was lower and in 4 it was higher than the expected value. In other words: with 2/3 of the characters the Ivád population showed a variation smaller than the norm for the *Homo sapiens*. This finding suggests a relative homogeneity of the population examined, but statistical judgement requires a more precise method. The significance of the difference between the observed and expected variance is tested by the following formula:

$$\chi^2 = \frac{n \cdot s^2}{\sigma^2}$$

(see column 3). Because of the high number of degrees of freedom the transformation given in column 4 must be used, that follows a normal distribution around a mean of zero, with unit standard deviation. As may be seen, the values obtained have a positive or negative sign, corresponding to the higher or lower value of the variance observed, as related to the expected value. From this it logically follows that the test puts the question one-sidedly. If we want to know only the probability of a deviation in the given direction, the critical value belonging to the 5 per cent level of significance is reduced from 1.96 to 1.64. In the last column of the table the probabilities determined in this way are presented.

At the usual levels of significance a deviation is demonstrable in 5 out of 12 cases; with 3 characters variance is smaller, with 2 it is greater than the expected value. Thus, although in a lesser measure, the tests show the same trend of decreasing variation as the simple comparison. Further considerations corroborate this judgement. With 3 other characters the variance observed remains at the 10 per cent level, lower than the expected value; with the larger sample the decrease would certainly be demonstrable even by more rigid criteria. It is important to note that the decrease is the most conspicuous in just those properties (such as, e.g., nasal breadth) which have been shown to be highly heritable by twin studies (*Verschuer*, 1931/32). Adding up the chi squares and the degrees of freedom, it may be stated that the aggregate of metric characters shows at the 5 per cent level of significance a variance lower than the expected one, though this result may be influenced also by the intercorrelations. Taking into consideration all of the evidence, our judgement may be summed up as follows: the Ivád population, as compared with the human norm, *shows a slightly narrowed variation* as regards anthropometric characters.

This is a rather unexpected result. A drift effect is unlikely, and at any rate *Dahlberg* (1943) showed that the diminution of variation caused by inbreeding takes a much slower course with the polygenic characters, than with the properties of simpler heredity. The counter-experiment (*Trevor*, 1953), too, indicates that in the case of crossing distant races the expansion of variation is not of such a great measure as would be naively expectable. Absolutely hypothetically, we suggest an explanation with selective factors. We have assumed that a non-specific homozygozity extending to many loci existent in the majority of the population would produce an increased

fragility of the organism, reducing the *general* resistance to exogenous stresses and their sequelae. In this situation the selective value of the genes influencing *specific* resistance may enormously increase and the *s*-coefficient has an extremely high value. The increased selective pressure resultant from this combination will cause, with the appropriate properties, a narrowing of variation, extreme means or modes. (According to the immunological studies of *Backhausz and Nemeskéri* [to be published in 1961], in the Ivád population, as compared with the control groups, the titres of antibacterial antibodies show a narrowed variation and shifted modes). Very close linkage or pleiotropy may extend the effect to other, phenotypic characters.

It may be mentioned here that the people living in Ivád differ from the inhabitants of near-by villages in one, highly heritable character. The population is characterized by having big ears. The mean physiognomic ear length with males is 63.35 ± 0.42, with females 58.02 ± 0.32 mm.

Summary

1. Ivád is an isolated village in the mountaneous area of North Hungary. Two-thirds of its inhabitants belong to the family Ivády, living there for more than 250 years. In the period 1940–1942, at the time of study, the population numbered 564 small farmers. Isolation had begun in the second half of the 18th century and developed fully in the mid-19th century, as a result of geographic and economic effects.

2. By European standards, the population of Ivád is an endogamous one, characterized by an increasing tendency to marry distant blood relations. In the period 1866–1916 the isolate numbered about 190 persons, with the mean inbreeding coefficient 28×10^{-4}.

3. Data are presented as to the phenotypic and gene frequencies for the ABO system and D factor. In these respects, no significant differences were noted between the population of Ivád and the control populations.

4. The demonstrably high rate of infant mortality is due in part to genetic factors as well. Both an increased, general autosomal homozygozity and an action of sex-linked, recessive, lethal factors seem to play a role.

5. The frequency of twinning was higher than the value characteristic for Hungary. This phenomenon is observable first of all among the non-Ivády persons living in the village.

6. The anthropometric characters show a slightly narrowed variation.

Résumé

1. *Ivád*, localité dans la Haute Hongrie montagneuse, est un village isolé. Deux tiers de sa population appartiennent à la grande famille *Ivády*. Entre 1940 et 1942, lors de l'enquête, la population y comptait 564 âmes, petits cultivateurs paysans. L'isolation de cette population a commencé dans la deuxième moitié du XVIII^{e} siècle, elle se précisa au milieu du XIX^{e} sous l'action des facteurs géographiques et économiques.

2. A l'échelle européenne la population d'Ivád passe pour endogame, et se caractérise par les mariages plus en plus fréquents entre des parents éloignés. Entre 1866 et 1916, la grandeur de l'isolat fut à peu près 190; le coefficient moyen de consanguinité y a été 28×10^{-4}.

3. Nous présentons les fréquences phénotypiques et géniques se portant sur le système ABO et sur la facteur D. Sous ce rapport il ne se montrait pas de différences significatives entre la population d'Ivád et de la population de ses environs.

4. La considérable mortalité infantile y a été provoqué aussi par des causes génétiques. Tant l'action de la homozygosité autosomale accrue et générale, que celle des facteurs létaux recessives, liés au sexe, sont démontrables.

5. La fréquence des accouchements de jumaux montre en ce lieu une valeur bien plus élevée que la valeur caractérisant sous ce rapport la population entière de la Hongrie. Ce phénomène se présente premièrement parmi les membres des familles non Ivády du village.

6. Les caractères anthropométriques montrent une variation légèrement rétrécie.

Zusammenfassung

1. *Ivád* ist ein im Berggebiet Nordungarns isoliert gelegenes Dorf. $^{2}/_{3}$ seiner Bevölkerung gehören zu der seit 250 Jahren dort ansäßigen Großfamilie *Ivády*. Zur Zeit der statistischen Aufnahme in den Jahren 1940–1942 betrug die Bevölkerung 564 Personen, die als Kleinbauern lebten. Die Isolation begann in der zweiten Hälfte des 18. Jahrhunderts durch den Einfluß geographischer und wirtschaftlicher Faktoren.

2. In europäischer Beziehung ist die Population von Ivád endogam, gekennzeichnet durch die zunehmende Heirat der entfernten Blutsverwandten untereinander. Zwischen 1866 und 1916 betrug die Größe des Isolats etwa 190, der mittlere Inzuchtkoeffizient 28×10^{-4}.

3. Es werden die Gruppen- und Gen-Häufigkeiten für das ABO-System und den D-Faktor angegeben. Signifikante Differenzen zwischen der Bevölkerung von Ivád und der benachbarten Bevölkerung haben sich nicht gezeigt.

4. Bei der nachweislich hohen Säuglingssterblichkeit spielen auch genetische Ursachen eine Rolle. Sowohl die Aktion gesteigerter, allgemeiner, autosomaler Homozygotie, als auch diejenige geschlechtsgebundener, rezessiver Letalfaktoren erscheint wahrscheinlich.

5. Die Häufigkeit der Zwillingsgeburten ist höher als der zurzeit für Ungarn geltende Wert. Diese Erscheinung kommt besonders bei den im Dorfe wohnhaften Nicht-Mitgliedern der Ivády-Familie zum Ausdruck.

6. Die anthropometrischen Merkmale zeigen etwas eingeengte Variation.

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Address of the authors: Dr. J. Nemeskéri and Dr. A. Thoma, Department of Anthropology, Museum of Natural History, *Budapest*, VI., Bajza u. 39 (Hungary)

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From the Institute of Genetics, University of Helsinki, the Finnish Foundation for Alcohol Studies, and the Research Laboratories of the State Alcohol Monopoly (Alko), Helsinki, Finland

THE DETERMINATION OF ZYGOSITY IN A STUDY OF FINNISH TWINS

By LASSE SAMMALISTO

The determination of zygosity of twins has proved to be a difficult problem. The possibilities of error in the determination based on polysymptomatic traits, the hereditary basis of which are often unknown, have been pointed out by various authors (e.g., *Neel and Schull* 1954). A more exact approach to the question is thus needed and several investigators have, therefore, taken into account serological traits. These are well-defined traits, the hereditary mechanism of which is exactly known. The theory of this method has been precisely dealt with by *Smith and Penrose* (1955).

Owing to the wide scope of the twin study started by the Finnish Foundation for Alcohol Research – the material consists of all male twins born in the thirties in Finland, of whom over 1000 pairs are still alive – the use of serological traits presents certain difficulties. The twins were scattered over the country and it seemed to us that we could not obtain the information needed without going beyond our resources, both with regard to time and money. In searching for a more convenient procedure, therefore, we decided to combine the older polysymptomatic method and the modern serological one.

The idea was as follows. On the basis of polysymptomatic traits which are known to be to a great degree genetically determined, an arbitrary scoring system should be constructed, and the score obtained should express the superficial similarity of the members of each twin pair. As the material was unhomogeneous in comprising both monozygotic and dizygotic twins, it was expected that the curve of variation of the scores would be bimodal or at least skewed. This bimodal or skewed curve of variation could then be divided mathematically into the monozygotic and the dizygotic components. As it was reasonable to expect that the curves would to some extent overlap, our aim was to use the serological method to determine the

zygosity of the pairs in the area of overlap, and for control's sake, to a fraction of the pairs on both sides of the area of overlap.

Polysymptomatic Diagnosis

The traits chosen for the polysymptomatic diagnosis were the following:

1. *Superficial resemblance of the facial features* – From ordinary passport photographs the degree of physical resemblance of the features was estimated, a score with a range from .0 to 1.0 being used. For examples, see fig. 1 on page 253.

2. *Resemblance as judged by other people* – The subjects were asked if other people had failed to distinguish between them and their co-twins. The scoring was performed according to the following schedule.

Score	Persons who have failed to distinguish between the members
.3	Parents
.1	Teachers
.1	Friends
.0	No one

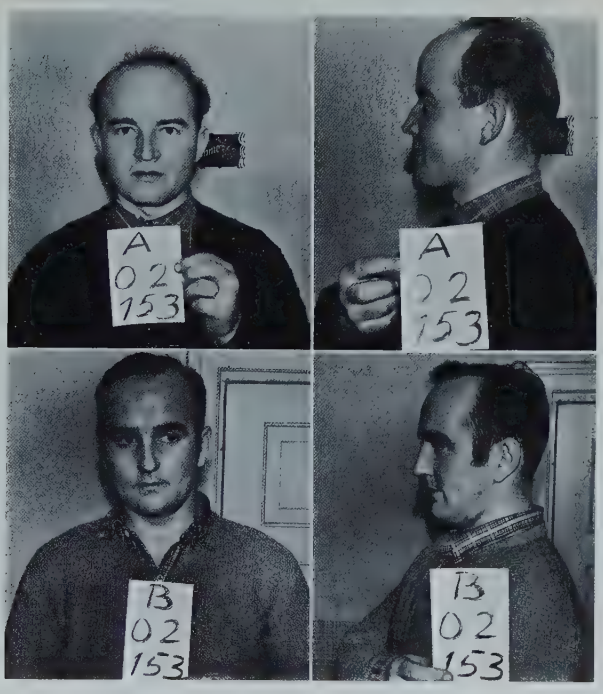
As the question was put to both members, the maximum score is 1.0.

3. *Height* – The height is expressed with an accuracy of 1 to 5 cm. The variation in accuracy is due to the ignorance of many subjects of their accurate height. Therefore, not as much weight could be given to height in the scoring system as would have been desirable. The scoring was performed according to the following schedule.

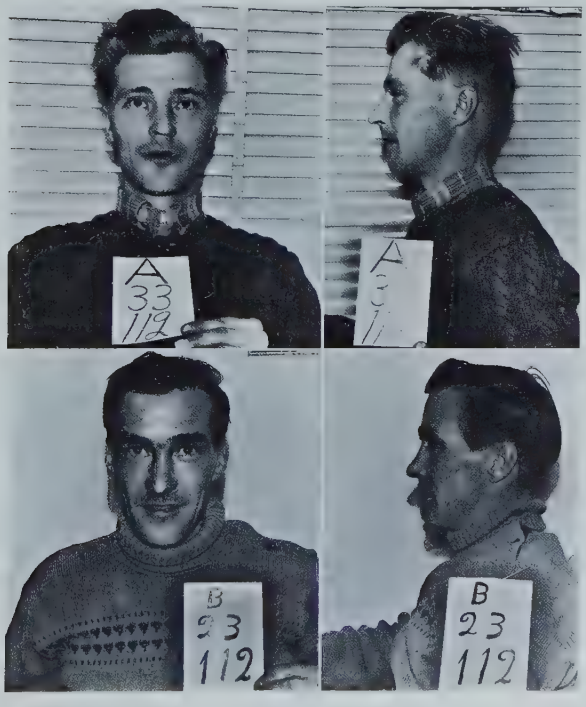
Score	Difference in cm.
.8	0–1
.5	2–3
.2	4–5
.0	6–

4. *Weight* – Here we meet the same difficulty as with height, since the persons in question did not know exactly how much they weighed. As weight is obviously more dependent on environmental influences than height, it was not regarded as very important in the diagnosis, as appears from the following scoring schedule.

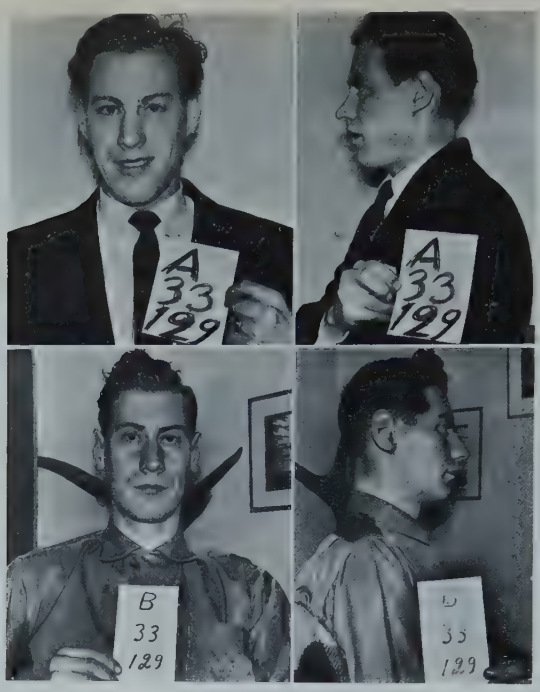
Fig. 1 Examples of scoring similarity of the facial features.



a) Score 0.1

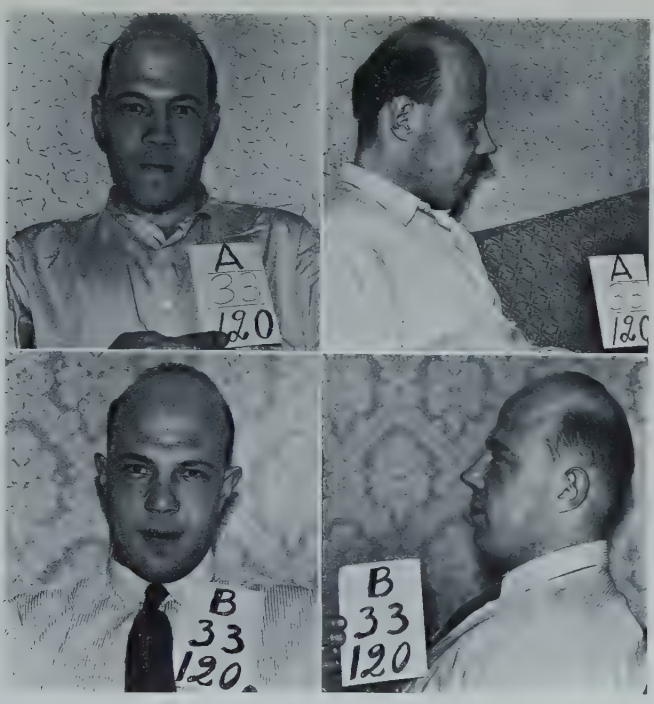


b) Score 0.3



c) Score 0.5

d) Score 0.7



e) Score 1.0

Score	Difference in kg.
.2	0–2
.1	3–4
.0	5–

5. *Eye colour* – This is a genetically fixed trait, but only the extremes, namely blue and brown, are clear-cut and easy to determine. The comparison is further complicated by the fact that the eye colour of the members of the same twin pair was often determined by different persons. In view of these difficulties, it was considered that the eye colour must not be accorded greater significance than that of the resemblance in the photograph. The scoring schedule used was as follows; the classes are 1. blue, 2. blue-grey, 3. grey, 4. grey-brown, 5. brown.

Score	Difference in classes
1.0	None
.8	1
.3	2
.0	3–

6. *Hair colour* – Each interviewer had a hair colour map for determinig the hair colour of the subjects. It comprised 11 nuances of colour ranging from black to natural blond. Red and grey remained outside this classification in the sense that if both had red or grey hair the score was 1.0 but if the one member had red or grey hair and the other not, the score was .0. Otherwise, the scoring schedule was as follows.

Score	Difference in hair colour classes
1.0	0
.7	1
.4	2
.1	3
.0	4–

7. *Hair form* – This includes only two categories, straight and curly. From this alone it follows that the trait cannot be regarded as very important in the polysymptomatic diagnosis. Similarity in the hair form has produced .3 points, dissimilarity none.

8. *Baldness* – Four degrees of baldness have been distinguished: none, beginning, considerable and complete baldness. Owing to the crudity of the scale and the handicaps in determination, complete similarity has added only .3 points to the score. A difference of one degree in the scale has added .1 points, and greater differences nothing.

9. *Site of the baldness* – The baldness can be situated on the forehead, on the crown or on the temples. Absolute similarity of site has produced .2 points, dissimilarity none.

10. *Skeleton* – This may be robust, normal or tiny. Absolute similarity has produced .3 points, dissimilarity none.

The total score can thus vary between .0 and 6.1. The scores actually observed varied between .8 and 6.1; the variation is seen from table 1 and from fig. 2. As expected, the curve is clearly skewed to the left, or towards the smaller scores. This supports the starting hypothesis that the scoring system is capable of separating the two kinds of twins at least partly.

The mathematical separation of the two components of the curve of variation has been performed according to the parabola method described by *Hald* (1952, pp. 152–158) in which the curve is converted to a semilogarithmic scale. The two curves of variation are seen from table 2 and from fig. 2.

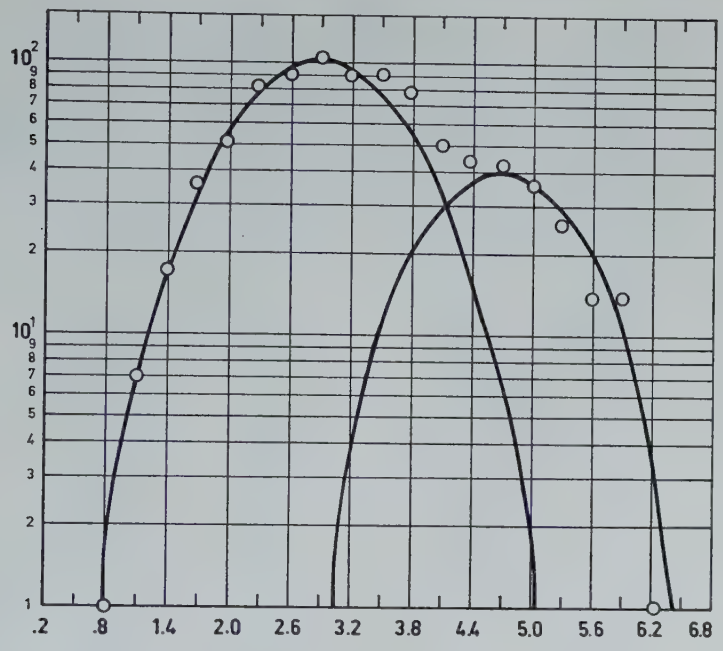


Fig. 2

The separation of the components in the curve of variation of the total scores. The curve of monozygotics smoothed from the frequencies in the table 2, right.

It is seen from the standard deviations of the two curves that, using the 95 per cent confidence interval, the curve of the dizygotics (to the left) falls between the limits 2.90 $\pm$ 1.75 and the curve of the monozygotics (to the right) between the limits 4.70 $\pm$ 1.58. It follows that the area of overlap lies between 3.12 and 4.65. For practical purposes this means that the pairs

within the range .8–3.1 can be regarded as dizygotic
within the range 3.2–4.6 must be identified serologically
within the range 4.7–6.1 can be regarded as monozygotic.

Because of the tentative character of the method used, the blood group method must be used as a control even outside the area of overlap. At the end of this report the agreement between the results obtained with this scoring system and with the serological method will be examined.

Serological Diagnosis

The following serological traits were included: ABO, MN and Rhesus blood groups and the haptoglobin 1–2 system. The Finnish frequencies of

the appropriate alleles in these systems, according to unpublished data of the Serological Institute, University of Helsinki, are as follows: ABO system: A_1 .20, A_2 .10, B .13, O .57; MN system: M .63, N .37; Rhesus system: R_1 .405, r .390, R_2 .140, R_0 .025, R″ .010, R′ .010; haptoglobins: hp_1 .36, hp_2 .64. The relative chances of dizygosity when the blood groups are the same are seen from the following tabulation, which has been calculated with the formulae given by *Smith and Penrose* (op. cit.).

ABO system		Rhesus system	
Twin pair both	Relative chance of DZ	Twin pair both	Relative chance of DZ
O	.69	C D E c	
A_1	.65	— — — +	.48
A_2	.48	— + — +	.37
B	.47	— — + +	.30
A_1B	.32	— + + +	.37
A_2B	.28	+ — — +	.35
		+ + — +	.45
MN system		+ — + +	.27
M	.67	+ + + +	.49
MN	.61	+ — — —	.25
N	.46	+ + — —	.43
		+ + + —	.42
Haptoglobins			
1–1	.68		
1–2	.61		
2–2	.45		

The initial odds in favour of dizygotic twins in Finland is not exactly known, but it is about 2 to 1, and in likeness of sex the relationship is inverse which gives by multiplication 1 to 1. These two probabilities can thus be omitted in calculating the total probability of monozygosity. This is calculated according to the formulae given by *Smith and Penrose* (op. cit.).

The probability of monozygosity in pairs with the same blood groups varies from .860 to .960 with a mean of .910, which is not as high a value as would have been desirable. Rarer antisera are not easily available in Finland, but in cases where the probability has been below .9 it has been raised by determining the P, Kell and Gm blood groups. These results, however, are not interesting in view of our methodological problem.

Table 1

The variation of the pairs according to the polysymptomatic score

Score	Frequency	Score	Frequency
.8	1	3.5	34
.9	–	3.6	26
1.0	2	3.7	23
1.1	3	3.8	35
1.2	2	3.9	20
1.3	3	4.0	13
1.4	2	4.1	21
1.5	12	4.2	16
1.6	8	4.3	17
1.7	17	4.4	11
1.8	11	4.5	16
1.9	16	4.6	15
2.0	15	4.7	17
2.1	21	4.8	11
2.2	27	4.9	8
2.3	22	5.0	15
2.4	32	5.1	13
2.5	26	5.2	12
2.6	28	5.3	11
2.7	37	5.4	3
2.8	32	5.5	4
2.9	45	5.6	9
3.0	30	5.7	1
3.1	34	5.8	6
3.2	29	5.9	4
3.3	28	6.0	4
3.4	33	6.1	1

Comparison of the Polysymptomatic and Serological Methods

The frequencies of serologically similar and dissimilar pairs for each score class in the polysymptomatic diagnosis is seen from table 3. It appears that the proportion of similar pairs increases steadily with increasing score. The increase is fastest at two points, of which one is at the score 3.2 and the other at 4.6, or exactly at the limits of the area of overlap of the curves of monozygotic and dizygotic twins. In the area of "certainly dizygotic" twins (see page 257) the percentage of similar pairs is only 7 which agrees well with the expected value (9 per cent). In the area of "certainly monozygotic twins" all but one are similar serologically.

Table 2

The separation of the curve of variation of the scores into its components

Score	Observed (total)	Calculated	
		dizygotic	monozygotic
.7– .9	1	1	–
1.0–1.2	7	6	(1)
1.3–1.5	17	16	–
1.6–1.8	36	32	(4)
1.9–2.1	52	56	–
2.2–2.4	81	78	(3)
2.5–2.7	91	96	–
2.8–3.0	107	107	–
3.1–3.3	91	96	–
3.4–3.6	93	78	15
3.7–3.9	78	56	22
4.0–4.2	50	32	18
4.3–4.5	44	16	28
4.6–4.8	43	6	37
4.9–5.1	36	1	35
5.2–5.4	26	–	26
5.5–5.7	14	–	14
5.8–6.0	14	–	14
6.1	1	–	1
Mean		2.90	4.70
Standard deviation		.7448	.6735

Table 3

The segregation of serologically similar and dissimilar pairs to different scores of polysymptomatic diagnosis

Polysymptomatic score	Blood group diagnosis		Relative chance in favour of dizygotic twins
	Similar	Dissimilar	
1.4–3.1	2	37	18.50
3.2–3.4	7	54	7.71
3.5–3.7	10	48	4.80
3.8–4.0	24	27	1.13
4.1–4.3	20	20	1.00
4.4–4.6	17	9	0.53
4.7–6.1	41	1	0.02

Relative Efficiency of Different Polysymptomatic Traits

It is interesting to find out which of the traits used in the polysymptomatic diagnosis have proved to be most useful in separating the curves of monozygotic and dizygotic twins. The mean score of serologically similar and dissimilar pairs for each polysymptomatic trait is seen from table 4. The relative efficiency of the traits has been got by dividing the difference mean of similar – mean of dissimilar by the maximum score of the trait in question.

Table 4

Relative efficiency of different polysymptomatic traits (for explanation, see also text)

	Photo-graph	Other people	Height	Weight	Eye colour	Hair colour	Hair form	Baldness	Site of baldness	Skeleton
Mean Similar	.799	.580	.529	.114	.852	.768	.286	.246	.148	.251
Dissimilar	.376	.143	.453	.080	.895	.699	.274	.224	.126	.234
Difference similar – dissimilar	.423	.437	.076	.034	–	.069	.012	.022	.220	.170
Maximum score	1.0	1.0	.8	.3	1.0	1.0	.3	.3	.3	.3
Relative efficiency of the trait (difference / max. score)	.423	.437	.095	.113	.0	.069	.040	.073	.073	.057

Overwhelmingly the best criteria have been the resemblance in photographs and resemblance as judged by other people. The efficiency of height, weight and hair colour is four to five times smaller than that of resemblance in photographs and in other people's judgment. It is not surprising that such traits as baldness, hair form and the structure of the skeleton have not added much to the accuracy of the diagnosis, as there are very few alternatives in their classification. The explanation of the lack of efficiency of the eye colour also lies in the crudity of the classification and in the handicaps of determination discussed on page 255.

A further point examined was whether it would have been possible to separate the two components efficiently enough by using the most efficient polysymptomatic traits only. The distribution of the scores attained by adding the scores of resemblance in photographs and in other people's judgment, height and weight, in the classes of dizygotic, uncertain and monozygotic twins as determined by the polysymptomatic method as a

whole are shown in table 5. It appears that the latter combination gives a result very close to that given by the polysymptomatic method as a whole. In fact, this combination is more efficient, since the area of overlap reaches only from the score .9 to 1.5, comprising 270 pairs, whereas using all ten traits, 350 pairs remained uncertain as to their zygosity.

Table 5

The segregation of DZ, uncertain, and MZ (as diagnosed by the polysymptomatic method as a whole) to different zygosity classes according to the most efficient traits (resemblance in photograph, in other people's judgment, height, and weight, maximum score is thus 3.0)

Score	DZ	Uncertain	MZ	Total
.0	1	–	–	1
.1	19	–	–	19
.2	43	–	–	43
.3	42	3	–	45
.4	39	6	–	45
.5	35	12	–	47
.6	38	12	–	50
.7	38	13	–	51
.8	30	13	–	43
.9	38	21	–	59
1.0	29	27	–	56
1.1	14	21	–	35
1.2	17	18	–	35
1.3	10	24	–	34
1.4	7	24	–	31
1.5	2	18	–	20
1.6	6	12	3	21
1.7	3	16	3	22
1.8	1	17	7	25
1.9	–	13	9	22
2.0	–	12	9	21
2.1	–	6	13	19
2.2	–	3	15	18
2.3	–	10	6	16
2.4	–	7	7	14
2.5	–	3	15	18
2.6	–	1	11	12
2.7	–	–	7	7
2.8	–	–	4	4
2.9	–	–	7	7
3.0	–	–	3	3

It thus seems as if the combination of the polysymptomatic and serological method achieves considerable success in practice. This procedure is often absolutely necessary when the number of subjects is large and they are scattered over vast areas. In any case the saving of expense is considerable, in particular if the material is large. In the present case, nearly 40 per cent of the pairs had to be tested serologically, but as appeared above, the efficiency of the polysymptomatic method can be improved by selecting the most efficient traits and perhaps also by adjusting the score values for each trait to produce the most effective separation of similar and dissimilar pairs. It would be desirable to test more traits with regard to their efficiency in separating the two classes of twins.

Summary

A method has been developed by which it is possible to determine the zygosity of a large sample of twins by a combination of the polysymptomatic and serological methods. This was made by a scoring system in which the score given for each of ten polysymptomatic traits increased with the similarity between members of a twin pair in these traits. The curve of variation of the total score was skewed, and the curve was separated to its two components, that of monozygotic and that of dizygotic twins. There remained an area of overlap of these components and the zygosity of the pairs in the area of overlap was determined by the serological method. The frequency of serological similarity in the pairs regarded as dizygotic on the basis of the score curve and the frequency of dissimilarity of the pairs in the monozygotic area of the score curve did not exceed expectation. Resemblance as judged by other people and resemblance in photographs were the best traits for effectively separating the two components of the curve.

Zusammenfassung

Ein neu entwickeltes Verfahren ermöglicht es, durch Kombination polysymptomatischer und serologischer Methoden die Eiigkeit bei großem Zwillingsmaterial zu bestimmen. Dies gelang mit Hilfe eines Berechnungssystems, bei dem der für jedes von 10 polysymptomatischen Merkmalen angegebene Wert mit der Ähnlichkeit der beiden Paarlinge in diesem Merkmal anstieg. Die Variationskurve des Gesamtwertes, die eine deutliche Schiefe aufwies, wurde in zwei Komponenten geteilt, den für eineiige und

den für zweieiige Zwillinge. An einer Stelle überschnitten sich diese beiden Komponenten, und so wurde hier die Eiigkeit der Paare mit der serologischen Methode bestimmt. Die Häufigkeit der serologischen Ähnlichkeit zwischen den auf Grund der Kurve als zweieiig angesehenen Zwillingen sowie die Häufigkeit der verschiedenen Paare in dem eineiigen Teil der Kurve überstieg nicht die Erwartungen. Von anderen Personen festgestellte Ähnlichkeiten und Ähnlichkeiten auf Photographien erwiesen sich als die besten Merkmale, um die beiden Teile der Kurve wirklich voneinander zu trennen.

Résumé

L'auteur développe une méthode pour le diagnostic des jumeaux uni- et bivitellins en combinant la polysymptomatologie et des tests sérologiques. Il s'agit d'un «scoring system» qui, pour dix traits polysymptomatiques, accorde des «points» qui augmentent avec la ressemblance des deux jumeaux. La courbe de variation obtenue par le total des points des dix traits est analysée et séparée dans ses deux composantes correspondant aux jumeaux uni- et bivitellins. Il reste une région de chevauchement et dans ces cas, le diagnostic était complété par des méthodes sérologiques. La fréquence de la concordance sérologique chez les paires isolées considérées comme dizygotiques et la discordance sérologique chez les paires considérées comme monozygotiques ne dépasse pas les valeurs prévues.

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Author's address: Dr. Lasse Sammalisto, Institute of Genetics, University of Helsinki, Pohj.-Rautatiekatu 13, *Helsinki* (Finland).

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From the Department of Psychiatry, University of Lund, Sweden, and the University Institute of Human Genetics, Copenhagen, Denmark

THE USE OF ANTHROPOLOGICAL TRAITS AND BLOOD GROUPS IN THE DETERMINATION OF THE ZYGOSITY OF TWINS

By S. J. DENCKER, M. HAUGE, L. KAIJ and A. NIELSEN

Siemens' so-called similarity method for determination of the zygosity of twins was much used without a satisfactory empirical basis before 1941, when *Essen-Möller* published an investigation in which he was able to prove that the intrapair similarity with regard to a number of anthropological traits is greater among undoubtedly monozygous (MZ) than among undoubtedly dizygous (DZ) twins of the same sex. On the basis of the findings in two groups of twins with known zygosity, viz. monochorionic (i.e. MZ) pairs and same-sexed pairs in which the partners had different blood groups (i.e. DZ) *Essen-Möller* was able to estimate the value of about a dozen anthropological traits in the determination of zygosity and indirectly also to what degree these traits are dependent upon genetic factors. This made it possible to express the validity of the zygosity diagnosis in any pair of twins numerically.

Since *Essen-Möller*'s investigation, a number of new serological characters have been discovered and their mode of inheritance has been established. The aim of the present investigation was to apply this new knowledge to *Essen-Möller*'s original sample, whereby the group of twins proved to be DZ would be extended considerably and the basis of evaluation ot the anthropological traits in the DZ group was thus amplified.

It seems convenient first to give a brief outline of *Essen-Möller*'s study.

Essen-Möller pointed out that although much supported the tenability of *Siemens*' method, particularly the works of *Schiff and Verschuer*, the correctness of the method could not be considered as proved. *Schiff and Verschuer* (1933) had shown that pairs with a high degree of anthropological similarity always had identical blood groups, while anthropologically non-

identical pairs had similar blood groups only with the frequency to be expected among siblings.

Essen-Möller divided his material into three groups, namely group I: undoubtedly MZ pairs, group III: undoubtedly DZ pairs and group II: twin pairs of uncertain zygosity, i.e. dichorionic pairs with identity as regards the blood group systems employed. Only same-sexed pairs were considered. Within these groups *Essen-Möller* determined the incidence of the various degrees of intra-pair difference with respect to a number of anthropological traits. In this way he was able to obtain a measure of the variation of the different characters in MZ and DZ pairs. The ratio between the incidence of the various degrees of difference in the pairs of groups I and III respectively could then be used to calculate the probability with which it is possible to allocate a given pair of group II to the MZ or DZ category.

In the numerical calculations of the validity of the zygosity diagnosis *Essen-Möller* utilized a formula derived by him and originally intended for application in paternity cases. This formula was worked out independently of a similar formula used by *Stocks* (1930) in the zygosity evaluation. If the frequency with which a given degree of difference (which may be zero) of a certain trait occurs in MZ pairs is called A, and the corresponding frequency in DZ pairs is called B, the frequency of monozygosity among all pairs with this degree of difference will be $W = A/A+B$, provided that there is an equal number of MZ and DZ pairs in the material under investigation.

If the frequency of a given degree of differences in more independent criteria in MZ pairs is A_1, A_2, A_3 etc. and in DZ pairs B_1, B_2, B_3 etc., then the proportion of MZ twins among all pairs of twins with this specific combination of differences will be

$$W = \frac{A_1.A_2.A_3\ldots}{A_1.A_2.A_3\ldots + B_1.B_2.B_3\ldots} = \frac{1}{1 + (B_1/A_1)\,(B_2/A_2)\,(B_3/A_3)\ldots}$$

In the ratio between DZ and MZ pairs in the original material is q the formula will be $W = 1/(1 + q(B_1/A_1)\,(B_2/A_2)\,(B_3/A_3)\ldots)$ which can be used in the calculation for every single pair. W thus expresses the probability of monozygosity calculated on the basis of the observed intra-pair differences in a number of traits.

The expression B/A gives the odds in favour of dizygosity in that it expresses how many times a given degree of difference is more common among DZ than among MZ twin pairs. The problem is then to find the value

of B/A for every possible degree of difference in the various anthropological traits. For blood groups and other characters of known genetic background which are uninfluenced by external factors, this ratio can be calculated directly by the use of the corresponding gene frequencies. For these properties, every phenotypical difference implies that the relative chance in favour of dizygosity is infinite when A is zero. A difference in such a character is, therefore, proof of DZ. In the same way, as the frequency of monochoria among DZ twins is zero, monochoria is proof of MZ. The value of B/A for anthropological traits other than blood groups can at present only be deduced empirically.

For his investigation, *Essen-Möller* used as his primary material all twins born at the Department of Obstetrics in Lund, Sweden, during the years 1900–1934. During that time the department was under the direction of one and the same obstetrician who personally examined practically all of the afterbirths. If gross examination left any doubt regarding the membranes, a milk test was performed, i.e. milk injected into an umbilical blood vessel indicated whether there was a common or separate circulation in the placenta.

The total number of full-term twins born during that period was 740 pairs which was 1.86 per cent of all deliveries in the clinic. The corresponds ing figure for the entire population in Sweden during the same period wa- 1.46 per cent. The difference, which is significant, is probably due to the fact that pregnant women with twins are more frequently referred to hospital for delivery.

The composition of the primary material appears from table 1. As expected, the frequency of monochorionic twins was lower than the frequency of MZ pairs as deduced from *Weinberg*'s formula. This can be explained by the assumption that some of the MZ pairs were dichorionic.

Essen-Möller confined his study to same-sexed pairs of which both twins were alive (total 236 pairs). Furthermore, the investigation was limited to those living in Skåne. For technical reasons, pairs below 5 years of age were excluded as well as pairs in which one or both twins were mentally defective, epileptic or had some mental disease. Two pairs refused to cooperate in the study. Otherwise the sample was unselected and comprised 178 same-sexed pairs. The twins were examined in their homes or at school. In 147 pairs both twins were examined at the same time and could be compared side by side. They were first studied for similarities regarding 79 anthropological traits. Each trait was classified according to the most common possibilities of variation. Finger prints were taken in the usual way

Table 1

Twin pairs born at the Department of Obstetrics, University Clinic of Lund, during the period 1900–1934. Distribution by sex and chorion.

	Male pairs	Female pairs	Total	Per cent
Monochorionic	50	64	114	15.4
Dichorionic				
same sex	158	160	318	43.0
diff. sex			294	39.7
Type of chorion unknown				
same sex	9	5	14	1.9
Total	217	229	740	

From *Essen-Möller* 1941.

and the total ridge count obtained. The reactions of the blood with anti-A, anti-B, anti-M and anti-N sera were determined. In addition, five photographs were taken of each twin: en face, profile, each ear separately perpendicular to the plane of the ear, and the face from below perpendicular to the plane of the floor of the nose. Finally, the examiner noted his own general impression of zygosity and also questioned the relatives about their impressions as to whether the twins belonged to the identical type or not. It should be stressed that the anthropological examination was performed without the examiner being aware of the results of examination of the membranes or of the blood groups.

In the final analysis of the material, *Essen-Möller* could use only the blood groups and 15 of the anthropological characters studied. The reason why the number was so limited was that the examination method proved too crude for a number of subtile similarities so that evaluation of them was not found to be sufficiently reliable when checked later on photographs, and that quite a number of characters were intercorrelated so that the use of the formula was impossible. In addition, *Essen-Möller* considered the comparisons of the iris, colour of hair and colour of skin too unreliable in those cases in which the twins had not been compared side by side. Only differences in total ridge count and the angle of the ears could be measured quantitatively. The complete findings appear from table 8 in *Essen-Möllers*'s paper (1941), to which the reader is referred. Some of the most important results are included in table 5 of this paper.

On the basis of this study it was possible to calculate the ratio B/A for every single trait and W for every pair of twins (cf. page 266). The distribution of W as found by *Essen-Möller* among the three basic groups of twins appears in table 3, column A, of this paper. It is evident that MZ twins resemble one another much more than DZ twins. This lends support to the justification of the polysymptomatic similarity test. It is also clear that the diagnostically uncertain group II occupies an intermediate position and may, therefore, be regarded as a mixture of MZ and DZ pairs, i.e. that dichorionic twins (groups II + III) include a larger number of DZ and a smaller number of MZ twins. This is, of course, no proof that there are two types of MZ twins.

Those pairs in groups I and III in which the findings differed from those expected are of particular interest. In group I 6 of 12 pairs with W less than 90 per cent could not be examined side by side which, as stated previously, excluded the use of two of the most valuable characters, i.e. iris and hair colour. In group III the similarity of the anthropological traits was very high in two pairs but the blood groups were found to be different (in pair no. 106 AB, M and AB, MN respectively, and in pair no. 107 they were O, MN and O, M). It was suggested, however, that this discrepancy might be ascribed to an inadequate serological technique.

Essen-Möller also accounted for his personal evaluation of zygosity (cf. table 5, column F, of the present paper) and for the diagnostic value of examination of the membranes and of the blood groups.

Present Investigations

Methods

In 1958 the twin pairs of groups I and II and pairs no. 106 and 107 were traced and asked to take part in a re-examination. Since group I is quite unique, it was considered a good opportunity to make a complete serological examination of monochorionic twin pairs. If one of those pairs were found to have different blood groups, this would contribute to the discussion on whether DZ twins can have a common chorion. Group II is the most interesting in this investigation. By means of the blood groups known at present the uncertainty as to the zygosity diagnosis of these pairs would be further reduced. This would in turn permit a more precise assessment of the diagnostic value of the anthropological traits.

The investigation consisted of interviewing the twins and taking a blood sample (of 5–10 ml of venous blood). A renewed anthropological examina-

tion was not considered worth while. At the same time the twins were questioned regarding their smoking habits, and the PTC taste reactions of the monochorionic pairs were determined. These examinations have been accounted for separately (*Friberg, Kaij, Dencker and Jonsson* 1959; *Dencker, Hauge and Kaij* 1959). The composition of the material included in the present investigation was as follows:

	Twin pairs of *Essen-Möller's*			
	Group I	Group II	Group III	Total
Re-examined	40	58	2	100
One of the partners dead at the time of the re-examination	2	2	–	4
Refused cooperation or not traceable	1	2	–	3
Total	43	62	2	107

Blood samples were thus obtained from 100 out of the 107 pairs which were originally intended to be included in the present study.

The blood was immediately sent to the laboratory for examination and if the blood could not be examined immediately on arrival it was kept in refrigerator. In a few cases where the subjects would not agree to venous puncture, capillary blood was collected, which excluded determination of the serum groups. The following antibodies were employed: anti-A, α_1, –B, –M, –N, –S, –C, –c, –D, –E, –e, –P, –Le^a, –K, –Lu^a and Fy^a. In addition, the Haptoglobins, the Gm(a) types and the isoantibodies were determined. The blood grouping was carried out without the examiner being aware of the identity of the person whose blood sample was under investigation. Owing to shortage of anti-Lu^a the determinations of the Lu^a-antigen had to be performed later and as far as possible only in pairs who were first found to be similar in all other systems.

Results

In five cases, the blood group determinations differed from the results obtained by *Essen-Möller*. Three cases had been regarded as doubtful (no. 001, 029 and 106) already by *Essen-Möller*. One pair (095) was found to belong to group A_2B and A_2B, as compared with B and B formerly. In pair no. 104, which was found by *Essen-Möller* to have identical blood groups a difference was now apparent in the ABO-system, which was confirmed on repeated examinations. On the other hand, the MN groups of pair no. 107, which *Essen-Möller* gave as doubtful, could be confirmed.

All monochorionic pairs tested showed complete identity in the blood groups studied.

As a result of the present investigation group III has been increased considerably as 35 pairs (formerly belonging to group II) were found to have different blood groups, but one of the pairs originally allocated to group III (pair no. 106) had to be transferred to group II as they presented identical blood groups. The final number of pairs in group III is thus 107. Group I contains, as before, 43 pairs. No blood samples could be obtained from three pairs (no. 003, 036 and 039), but as they were all known to be monochorionic, they are still to be considered as definitely monozygous and will, therefore, be included in some of the analyses to follow.

24 of the dichorionic pairs examined during the present study showed identity as to all the blood groups investigated, and consequently, they form group II. Finally, 4 dichorionic pairs (no. 069, 071, 087 and 104), which were found by *Essen-Möller* to have identical ABO- and MN-groups, could not be re-tested, and as it is thus unknown whether they are identical or different with regard to the remaining blood groups, they will have to be left out of account.

As group III has now been increased considerably, a broader basis for evaluation of the anthropological criteria has been established. The values of B/A and of W have, therefore, been recalculated. Table 2 gives a survey of all the 15 characters mentioned above as well as B/A and its logarithms for more simple practical use. Furthermore, the probability of monozygosity, W, has been calculated for each degree of intra-pair difference for every single character, and finally a number indicating the diagnostic value of each trait is to be found in the table.

The distribution of the material according to the final probability of monozygosity in the three basic groups of twin pairs is given in Table 3. The calculation has first been based on traits nos. 1–3 as these are obviously in a class by themselves. Secondly, the probability has also been calculated on the basis of these three traits as well as the blood groups.

Discussion

The present material may be regarded as a random sample apart from the fact that all twins were born at one and the same clinic and that the review was limited to only part of the geographical region covered by the primary material. These limitations, however, can hardly affect the present analysis.

A comparison of the distribution of the twin pairs obtained by various methods of classification seems to be of interest and is given in table 4. Those pairs for which the calculated total probability of mono- or dizy-

Table 2

Distribution of twins pairs for 15 anthropological traits

No.	Trait	A	B	C	D	E	F	G
1.	*Colour and structure of iris	D	73	0	28.4	3.4	1.4534	18.5–81.5
		S	17	35	0.19	83.7	0.2787–1	
2.	*Colour of hair	D	69	5	5.36	15.7	0.7292	30.4–69.6
		S	21	30	0.27	78.6	0.4314–1	
3.	Total ridge count.	40+	41	0	430	0.2	2.6335	29.0–71.0
	Intra-pair difference	30–39	11	0	9.69	9.4	0.9863	
		20–29	10	6	1.55	39.2	0.1903	
		10–19	20	12	0.47	68.4	0.6721–1	
		0– 9	19	24	0.26	79.2	0.4150–1	
4.	Upper angle between ear	20°	8	0	10.9	8.4	1.0374	42.0–58.0
	and head. Intra-pair	10–20°	27	2	5.59	15.2	0.7474	
	difference between means	5–10°	31	10	1.27	44.1	0.1037	
	of right + left angles	0– 5°	39	31	0.51	66.0	0.7075–1	
5.	*Incisura intertragica	D	29	0	12.0	7.7	1.0792	43.7–56.3
		S	76	43	0.74	57.4	0.8692–1	
6.	*Tragus	D	17	0	7.04	12.4	0.8476	47.1–52.9
		S	88	43	0.86	53.8	0.9345–1	
7.	Presence of whorls	D	39	6	2.62	27.6	0.4183	46.5–53.5
		S	65	36	0.73	57.8	0.8633–1	
8.	Freckles	D	17	1	7.00	12.5	0.8451	47.0–53.0
		S	84	40	0.85	54.0	0.9294–1	
9.	Attachment of ear lobe	D	22	2	4.47	18.3	0.6503	47.1–52.9
		S	83	41	0.83	54.7	0.9191–1	
10.	*Colour of skin	D	13	0	5.21	16.1	0.7168	47.8–52.2
		S	74	35	0.88	53.3	0.9445–1	
11.	*Bridge of nose	D	6	1	3.36	23.0	0.5263	48.0–52.0
		S	26	17	0.86	53.8	0.9345–1	
12.	Outer edge of helix	D	7	0	2.91	25.6	0.4639	49.4–50.6
		S	98	43	0.95	51.2	0.9777–1	
13.	Size of lips	D	15	4	1.55	39.2	0.1903	49.7–50.3
		S	89	39	0.94	51.4	0.9731–1	
14.	Tuberculum posterior auris	D	6	0	2.60	27.8	0.4150	49.5–50.5
		S	87	40	0.96	51.0	0.9823–1	
15.	Shape of nostrils	D	13	3	1.76	36.2	0.2455	49.6–50.4
		S	91	39	0.94	51.5	0.9731–1	

Column A: type of intra-pair variation: D = difference, S = similarity

B: number of unquestionably dizygous pairs with stated type of variation (pairs belonging to group III as defined by the present blood group determinations)

C: number of unquestionably monozygous pairs (group I) with stated type of variation

Table 3

Distribution of the twin pairs according to the calculated probability of monozygosity

Calculated probability of monozygosity	Group I-pairs			Group III-pairs			Group II-pairs		
	A	B	C	A	B	C	A	B	C
1.0–0.99	15 (+1)	0	26	1	0	–	1 (+1)	0	14
–0.95	9 (+1)	25	4	0	3	–	9 (+4)	9	1
–0.90	4 (+1)	0	0	1	0	–	0 (+1)	0	0
–0.50	5 (+5)	10	0	0 (+1)	6	–	3 (+4)	6	0
–0.10	0 (+2)	0	0	3 (+7)	4	–	1 (+2)	0	1
–0.05	0	0	0	1	1	–	2	0	0
–0.01	0	0	0	6 (+3)	17	–	4 (+3)	1	0
– 0	0	0	0	45 (+5)	54	85	18 (+9)	0	0
Total	33 (+10)	35	30	57 (+16)	85	85	38 (+24)	16	16

Group I: unquestionably monozygous pairs (monochorionic)

III: unquestionably dizygous pairs (with blood group difference between the partners)

II: dichorionic twin pairs with partners of identical blood groups

In column A the grouping is based on determinations of the A, B, O, M and N antigens only as carried out by *Essen-Möller* (1941). In columns B and C the grouping of the twin pairs has been done in accordance with the results of the present extended blood group determinations.

Column A: probability calculated on the basis of traits no. 1–15 (cf. table 2). The figures in brackets indicate the number of twin pairs in which one or more of the traits no. 1–10 have not been studied

Column B: probability of monozygosity calculated on the basis of traits no. 1, 2 and 3 only

Column C: calculation based on traits no. 1, 2, 3 and the present blood group determinations

(Explanation to Table 2 continued)

D: calculated value of B/A; for further explanation see page 266

E: calculated value of W in per cent (cf. page 266)

F: log B/A

G: figures indicating the diagnostic value of the trait: the first figure gives the percentage of misclassifications in a hypothetical group of proven MZ pairs when classified only by means of the trait mentioned; the second figure indicates the percentage of correct classifications

The numbers of the traits are the same as used by *Essen-Möller* (1941).

* Indicates that the trait should only be taken into account if the partners are compared side by side.

Table 4

Comparison between the distribution of twin pairs obtained by use of various classification methods

Basic grouping	Estimate of zygosity	Classification method			
		A	B	C	D
Group I	(MZ)	24	25	29	33
	uncertain	9	10	5	10
	(DZ)	0	0	6	0
Incompletely examined		10	8	3	0
Total		43	43	43	43
Group III	(MZ)	0	3	0	0
	uncertain	8	11	0	5
	(DZ)	71	71	96	102
Incompletely examined		28	22	11	0
Total		107	107	107	107
Group II	(MZ)	11	9	16	17
	uncertain	2	6	4	4
	(DZ)	1	1	3	3
Incompletely examined		10	8	1	0
Total		24	24	24	24

Group I: unquestionably MZ pairs (monochorionic)
Group III: unquestionably DZ pairs (with blood group difference between the partners as found by the present determinations)
Group II: dichorionic pairs with blood group identity between partners (as found by the present investigation)
Classification methods: A: probability of monozygosity calculated on the basis of traits no. 1–10 or more (cf. table 2)
B: based on traits no. 1–3 only
C: judgment of the relatives of the twin pair
D: *Essen-Möller's* impression of zygosity based on the outer appearance of the twins

gosity reached 0.95 or more were assigned to the classes labelled "(MZ)" and "(DZ)" respectively, the remainder to the class "uncertain". It is obvious from this table that the number of pairs assigned to the wrong class by use of all the anthropological traits is not large, but about 15 per

cent of the twin pairs cannot be classified with a reasonable degree of certainty, i.e. with a probability of at least 0.95. There appears to be a greater proportion of MZ twin pairs than of DZ twin pairs which cannot be classified.

If the classification is based solely on the first three traits it will result in a larger number of unclassifiable pairs than with the use of all the anthropological characters, besides which a few DZ pairs will be wrongly classified. The conclusion to be drawn is that a careful simultaneous examination of both partners will permit a fairly valid diagnosis in the majority of cases, but if the criteria are very rigid, many of the pairs, preferably MZ, will be unclassifiable and therefore not lend themselves to special genetic studies, for example. Furthermore, it must be kept in mind that in no case is the zygosity diagnosis to be considered as proved. It should also be stressed that the calculation of the probability of monozygosity can only be carried out if the variation within the two types of twins is known regarding the traits used in the population from which the twins emanate. Furthermore, the use of anthropological traits is time consuming but the greatest practical difficulty is that the members of each pair must be examined side by side, since about half of the traits can only be assessed with confidence in this way. Finally, the possible influence and importance of age variations is unknown and cannot be elucidated by means of the present material.

The value of the serological examinations alone is apparent from the fact that 107 of the 172 twin pairs which had been blood grouped to a satisfactory extent were proven to be DZ. Blood grouping does not only provide proof of dizygosity, but also the probability of monozygosity in identical pairs can always be calculated without the extensive special previous examinations necessary for the anthropological traits as described above. Provided that the gene frequencies of the blood group systems are known in the population to which the twins belong, it is easy to calculate this probability. Formulae for this purpose have been given by *Levit and Soboleva* (1935), *Essen-Möller* (1941), *Smith and Penrose* (1955) and *Sutton, Clark and Schull* (1955).

The basic grouping of the twin pairs in the present sample (according to blood groups and chorion) is thus 107 proven DZ pairs, 43 proven MZ pairs and 24 dichorionic pairs of identical blood groups. If the latter 24 pairs are classified according to the total probability of monozygosity, calculated on the basis of the blood groups and anthropological characters studied, 20 pairs must be considered as probably monozygous as they have a probability of monozygosity of at least 0.98. For the remaining four pairs this

probability is 0.913 (pair no. 066) and 0.045 for pair no. 080 for which no data were available about the iris or the colour of the hair, which makes the calculation incomplete in comparison with the major part of the material. For pair no. 083 finger prints were not available; here the total probability of MZ was 0.080. Finally, one pair (no. 078) was found to have a MZ probability of 0.467. It therefore appears reasonable to regard the 107 proven DZ pairs plus pair no. 080 (for which the DZ probability was more than 0.95), thus altogether 108 pairs, as DZ, 3 pairs as uncertain and 63 pairs as MZ with a MZ probability of more than 0.98. If the uncertain pairs could have been examined further it would probably be possible to make a firmer diagnosis in these cases also.

To check whether the number of probably DZ pairs observed, i.e. 107 + a maximum of 4 pairs, fill the thoretical expectation, the latter may be calculated provided that a) the number of proven DZ pairs is known, b) the material is representative and c) the distribution in DZ twins of blood groups does not differ from that of the general population (*Juel-Nielsen, Nielsen and Hauge*, 1958). The number of DZ pairs expected is 107/(1—P) where P is the calculated combined probability of blood group identity between two siblings with respect to all the systems used here. This value amounts to 109.9 pairs with the upper (95 per cent) confidence limit 110.7. The agreement with the number of DZ pairs observed is good. This thus considerably strengthens the assumption that some of the MZ twin pairs are dichorionic. The proportion of dichorionic pairs among all MZ pairs may be estimated to be about 30 per cent and the proportion of MZ among all dichorionic same-sexed pairs about 15 per cent. The number of MZ pairs among all same-sexed twin pairs in this sample is between 63/174 and 67/174 or 36.3–38.5 per cent. These figures are used in the calculation of the above mentioned factor q (see page 266) included in the formula for the calculation of the total probability of monozygosity. *Essen-Möller* found that the proportion of MZ among same-sexed pairs was fairly constant within the age groups studied by him and around 0.38. The mortality noted in groups I and II in the course of the last 20 years gave no reason to revise this opinion, and the value of $q = 1.6$ has been used in the present calculations.

A very important problem which has often been discussed is whether the intra-pair difference is on the average greater in monochorionic than in dichorionic MZ pairs, e.g. with respect to the total external appearance. This problem may be elucidated but not solved by means of the findings in the present material. Since it is unknown which of the 24 dichorionic pairs

of identical blood groups are DZ, no exact analysis is possible. If *Essen-Möller*'s general evaluation of the zygosity of the twin pairs is taken as an expression of the general external similarity, and this is used to elucidate the problem mentioned, the following results appear, where grade 1 indicates very marked similarity, grade 2 marked difference (only pairs in which the partners were examined side by side being included):

Grade	1	1?	2?	2
No. of monochorionic pairs	30	3	2	0
No. of dichorionic pairs with identical blood groups	17	3	1	3

These figures provide no support for the assumption of any greater intra-pair difference as regards external appearance in monochorionic than in dichorionic MZ twin pairs.

In practice, under certain conditions, e.g. if one of the twin partners is not living at the time of an examination, it may be necessary to base the zygosity diagnosis on information obtained from relatives of the twins. To assess the value of such a procedure, the pairs of the present material were classified according to the opinion of the relatives regarding the zygosity and the results compared with the basic grouping (table 4, column C). The uncertain class is not very large but consists mainly of MZ pairs and, furthermore, a fair number of MZ pairs were wrongly diagnosed as DZ, whereas DZ are only rarely considered as MZ.

Finally, it may be of interest to study the reliability of the estimate of zygosity made by an experienced research worker in this field. Column D of table 4 gives *Essen-Möller*'s personal opinion concerning the pairs studied side by side. The true percentage error is very small, but about 10 per cent of the pairs could not be classified with satisfactory confidence, and in this group MZ twins were predominant. It should be recollected that the reliability of this diagnostic method can only be judged if all evaluations are made by one and the same examiner.

Conclusions. Practical performance of zygosity determination

On the basis of the investigations presented here, it may be concluded that complete examination of the serological characters is the most valuable and reliable means for diagnosting zygosity. These traits alone permit definite diagnosis in a high percentage of cases: with the blood groups used in the present examination more than 95 per cent of the same-sexed DZ pairs could be distinguished with certainty. The method can also be used for

Table 5

Survey of the re-examined part of *Essen-Möller's* material

Pair No.	A	B	C	D	E	F	G	H	J
Group I									
001	23	M	+	+	1	id	99.6	97.9	99.9
002	17	F	+	+	0	id	99.6	97.9	99.9
004	29	F	+	+	1–6	id	99.6	97.6	99.8
005	35	F	+	+	2	id	99.6	97.9	99.9
006	7	F	+	+	3	id	99.6	97.9	99.9
007	5	F	+	+	4	id	99.6	97.9	99.9
008	7	F	+	+	7	id	(99.5)	97.9	99.9
009	18	F	+	+	19	id	99.3	96.2	(99.8)
010	7	F	+	+	19	id	99.3	96.2	99.9
011	8	F	+	+	13	id	99.3	96.2	99.8
012	7	F	+	+	10	id	99.3	96.2	99.8
013	21	M	+	+	2	id	99.1	97.9	99.9
014	6	F	+	+	1	id?	99.1	97.9	99.9
015	12	M	+	+	4	id	99.1	97.9	99.9
016	5	M	+	+	4	id	99.1	97.9	99.9
017	12	F	+	+	7	id	98.7	97.9	99.8
018	23	F	+	+	17	id	98.5	96.2	99.8
019	13	F	+	+	7	id	98.1	97.9	99.9
020	7	F	+	+	13	id	(98.0)	96.2	99.8
021	10	F	+	+	8	id	98.0	97.9	99.9
022	5	M	+	+	23	id	97.9	88.7	99.7
023	14	M	+	+	20	id	97.9	88.7	99.5
024	9	F	+	+	22	id	97.9	88.7	99.6
025	6	F	+	+	15	id	97.8	96.2	99.7
026	22	F	+	+	2	df?	97.5	97.9	99.8
027	10	F	+	+	4	id	94.8	97.9	99.9
028	17	M	+	+	21	id	94.5	88.7	99.5
029	24	F	..	..	1	id?*	(93.5)	—	(98.9)
030	6	F	+	—	2	id	92.4	70.2	(95.7)
031	34	F	+	+	23	id	91.4	88.7	(99.2)
032	7	F	+	—	16	id?	87.2	56.6	98.0
033	37	F	..	..	4	id*	(86.4)	—	(98.7)
034	18	F	..	..	9	id?*	(86.4)	—	(98.3)
035	7	F	+	—	13	id	86.2	56.6	97.2
037	13	M	..	..	7	id*	(85.2)	—	(99.2)
038	30	F	..	..	12	id*	(78.3)	—	(97.5)
040	15	M	+	—	12	id?	75.4	56.6	97.1
041	9	M	+	—	3	id	61.5	70.2	98.9
042	17	M	..	..	14	df?*	(37.7)	—	(97.1)
043	9	M	..	..	23	df?*	(26.3)	—	(93.4)

Pair No.	A	B	C	D	E	F	G	H	J
Group II									
044	5	M	+	+	3	id	99.6	97.9	99.9
045	15	F	+	+	9	id	(99.5)	97.9	99.9
046	24	F	+	+	..	id	(98.3)	—	(99.6)
047	5	M	+	+	15	id	98.3	96.2	99.8
048	6	F	+	+	13	id	98.2	96.2	99.8
049	5	F	+	+	..	id	(98.1)	—	(99.8)
050	10	F	+	+	23	id	98.0	88.7	99.6
051	13	F	+	+	22	id	98.0	88.7	99.5
052	17	F	+	+	12	id	(97.8)	96.2	99.9
053	15	M	+	+	7	id	97.2	97.9	99.9
054	6	M	+	+	15	id	96.8	96.2	99.8
055	16	M	+	+	21	id	95.4	88.7	99.6
056	5	F	+	+	21	id	95.4	88.7	99.7
057	7	M	+	+	24	id?	95.4	88.7	99.7
059	21	M	..	..	4	id*	(93.5)	—	(99.0)
060	29	F	..	..	10	id?*	(89.0)	—	(98.0)
061	5	M	+	+	..	id	(79.7)	—	(99.7)
062	9	M	+	+	13	id	79.6	96.2	99.7
066	22	M	..	..	23	id?*	(53.4)	—	(91.3)
068	15	F	+	—	9	df?	23.1	70.2	98.3
078	28	M	—	—	2	df	1.4	1.5	46.7
080	24	M	..	..	44	df*	(0.4)	—	(4.5)
083	8	M	—	—	..	df	(0.07)	—	(8.0)
106	7	F	+	+	7	id	99.6	97.9	99.9
Group III									
058	4	F	+	+	..	df?	(95.0)	—	
063	26	M	..	..	28	df*	(73.8)	—	
064	12	M	+	+	12	df	68.1	96.2	
065	12	F	+	—	2	df	55.2	70.2	
067	3	F	+	—	..	df	(25.6)	—	
070	8	F	—	—	9	df	8.4	1.5	
072	7	F	—	—	5	df	4.1	1.5	
073	23	F	..	..	23	df*	(3.4)	—	
074	7	F	—	+	..	df?	(2.6)	—	
075	19	M	—	+	32	df	2.3	5.9	
076	23	F	—	—	5	df	(1.7)	1.5	
077	17	M	—	+	18	df	1.5	14.7	
079	6	F	—	+	17	df	0.7	14.7	
081	16	M	..	..	117	df*	(0.2)	—	
082	6	F	—	+	..	df	(0.1)	—	
084	22	M	—	—	14	df	0.04	0.8	

Pair No.	A	B	C	D	E	F	G	H	J
085	10	M	—	—	14	df	0.04	0.8	
086	15	M	..	..	100	df*	(0.03)	—	
088	11	M	—	—	11	df	0.01	0.8	
089	6	F	—	—	51	df	0.01	0.0009	
090	8	F	—	+	58	df	0.008	0.01	
091	13	F	—	—	26	df	0.007	0.2	
092	29	F	—	—	77	df	0.005	0.0009	
093	7	M	—	—	94	df	0.004	0.0009	
094	4	M	—	—	53	df	0.004	0.0009	
095	14	F	—	—	105	df	0.004	0.0009	
096	35	F	..	..	61	df*	(0.004)	—	
097	8	F	+	—	94	df	0.003	0.1	
098	7	M	—	—	..	df	(0.002)	—	
099	12	M	—	+	63	df?	0.002	0.01	
100	10	F	—	—	8	df	0.001	1.5	
102	14	F	—	—	47	df	(0.0006)	0.0009	
103	12	M	—	—	50	df	0.0003	0.0009	
104	15	M	—	—	42	df	0.0003	0.0009	
105	13	F	—	—	30	df	0.0002	0.04	
107	5	F	+	+	9	id?	94.8	97.9	

Explanation of symbols:

Groups I, II and III defined as in table 4. The numbers given to the twin pairs agree with those used by *Essen-Möller* (1941) in his table 8.

Column A: age of twins at the first investigation (by *Essen-Möller*)

B: sex, M = male, F = female

C: intra-pair similarity as regards the iris

D: intra-pair similarity as regards hair colour

E: total ridge count difference between partners

F: *Essen-Möller*'s evaluation of the zygosity diagnosis, based on the external appearance only: id = probably MZ, df = probably DZ. Asterisks indicate that the partners have not been seen side by side

G: probability of monozygosity calculated on the basis of all the anthropological traits investigated (excluding blood groups)

H: probability of monozygosity calculated on the basis of traits no. 1, 2 and 3 only (see table 2)

J: probability of monozygosity calculated on the basis of the same traits as in column H + the information from the present blood group determinations

Brackets are used to indicate that information is incomplete as to one or more anthropological and/or serological traits.

.. means no information

pairs not examined simultaneously. The probability of monozygosity can be assessed for each pair of twins on the basis of the gene frequencies in the corresponding population. These frequencies are at present known with sufficient accuracy in most places. In this respect the anthropological traits other than blood groups offer much greater difficulties.

Since circumstances may somethimes make it necessary to limit the number of blood group systems used, it might be mentioned that in the present investigation the ABO, MN and Rh-systems alone would have permitted a diagnosis of DZ in about 85 per cent of all the DZ pairs diagnosed as such by means of blood groups. If, in addition, the Duffy *or* Gm *or* Hp system had been used a further 6–7 per cent DZ pairs could have been distinguished. If, in addition to the ABO, MN and Rh-systems, use is made also of both the Duffy and the Gm system, a diagnosis could have been made in about 95 per cent. These empirical findings agree with the theoretical expectations.

When only anthropological traits other than blood groups are used a diagnosis of dizygosity could never be made with certainty for any of the pairs. On the other hand, these characters are useful diagnostic supplements. For populations with a distribution of these traits corresponding to that in the south of Sweden, the values of B/A given in table 2 can be used directly in the calculation of the probability of monozygosity.

By employing the blood groups in determining the zygosity diagnosis, the group of DZ pairs sorted out in this way is pure, whereas the group of probably MZ pairs is mixed and includes a proportion of DZ pairs which may, however, be estimated. If only anthropological characters other than blood groups are used in the calculation of the MZ probability, or the judgment of the twin pairs themselves or their relatives, or the evaluation made by an experienced research worker is taken as the basis of classification, an essential part of the twin pairs cannot be classified with satisfactory certainty, and among these unclassifiable pairs the majority seems to be MZ. Furthermore, both the resulting classes (of probably MZ and probably DZ pairs respectively) will usually be mixed. The extent of the admixture of wrongly classified pairs cannot be estimated. According to the present investigation it seems to be mainly MZ pairs which are wrongly classified.

In future investigations of larger series of twins it would be useful if the most important anthropological traits could be examined, i.e. iris, hair colour and finger prints. In the present material, for example, no difference was found as regards the iris between monochorionic twin partners. A difference in the colour of the hair was noted in 5 – all adults – of 35 mono-

chorionic pairs investigated. The intra-pair difference in total ridge count did not exceed 30 in any of the monochorionic pairs. This is in agreement with previous observations in probably MZ pairs, for whom information concerning the membranes was not available (*Holt* 1952, 1954).

It would, therefore, be of value if at least these three criteria could be included in later examinations of twins, where the zygosity diagnosis is made by other means, in order to ascertain more fully the diagnostic value of these criteria. Elucidation of the genetic background of these and the other traits would probably increase the diagnostic value still more. Finally, it should be stressed that exact information on the membranes in twin births be noted routinely in the records. Monochoria is as yet the only practical proof of monozygosity and is present in the majority of monozygous twin pairs.

Summary

The present work is based on an unselected twin material originally collected and studied by *Essen-Möller* 20 years ago. From this material, *Essen-Möller* sorted out a group of proven monozygous pairs, diagnosed by the presence of monochoria, and a group of proven dizygous pairs of the same sex, distinguished by means of blood group differences. By studying the intra-pair similarities and dissimilarities as regards 15 anthropological traits in these two groups, *Essen-Möller* was able to provide the proof of the tenability of the polysymptomatic similarity test, and to express the diagnostic value of the 15 traits numerically.

By use of eight more blood group systems the present investigators increased the group of proven dizygous pairs considerably, thus extending the basis for determining the value of the anthropological characters in the zygosity diagnosis. It was found that expecially the iris, the colour of the hair and the finger prints give very valuable information, although an intra-pair difference does not give a definite proof of dizygosity as does a difference in blood groups. The use of many of the anthropological traits is limited because side by side comparison of the partners is necessary. Further, the numerical expressions of their diagnostic value given here do not apply to populations with a different distribution of the traits.

The blood groups, on the other hand, may provide a proof of dizygosity in more than 95 per cent of the same-sexed dizygous pairs if most or all of the systems are used. When the frequencies of the corresponding genes are known, as is the case in most countries, the probability of monozygosity in

same-sexed pairs of identical blood groups may be calculated without any special preceding twin investigations being necessary. Blood groups may also be used in twin pairs of which the partners cannot be examined at the same time or place.

A comparison between various diagnostic methods has been undertaken in order to give an estimate of the number and direction of misclassifications.

Zusammenfassung

Die vorliegende Untersuchung beruht auf einem Zwillingsmaterial, das vor 20 Jahren von *Essen-Möller* gesammelt wurde. Aus diesem Material wurde von ihm eine Gruppe sicher eineiiger Zwillinge, wo die Eiigkeitsdiagnose durch Monochorie gesichert war, und eine Gruppe sicher zweieiiger gleichgeschlechtiger Zwillinge, wo die Zweieiigkeit durch Blutgruppenverschiedenheit diagnostiziert worden war, ausgesondert.

Essen-Möller untersuchte die Variation von 15 anthropologischen Merkmalen in diesen zwei Gruppen und konnte die Haltbarkeit der polysymptomatischen Ähnlichkeitsdiagnostik beweisen und die Reihenfolge des diagnostischen Wertes dieser 15 Merkmale empirisch aufstellen.

Die jetzigen Untersucher konnten durch Gebrauch weiterer 8 Blutgruppensysteme die Anzahl der sicher zweieiigen Zwillingspaare bedeutend vermehren, und damit die Bedeutung des Wertes anthropologischer Merkmale in der Eiigkeitsdiagnose erweitern.

Man fand, dass Irisstruktur und -farbe, Haarfarbe und Papillarlinien der Fingerbeere sehr wertvolle Informationen geben können, obwohl ein Unterschied dieser Merkmale keinen Beweis der Zweieiigkeit liefern kann, wie es beim Unterschied der Blutgruppen der Fall ist.

Der Nutzen vieler Merkmale ist dadurch begrenzt, daß die Partner eines Zwillingspaares gleichzeitig untersucht werden müssen. Außerdem kann die Reihenfolge des diagnostizierten Wertes der hier angegebenen Merkmale nicht auf eine Bevölkerung mit einer anderen Verbreitung dieser Merkmale angewandt werden.

Die Blutgruppenbestimmung dagegen kann, wenn fast alle Systeme gebraucht werden, die Zweieiigkeit in mehr als 95% der gleichgeschlechtigen Zwillingspaare sichern. Wenn die Häufigkeit der entsprechenden Gene in der Bevölkerung bekannt ist, was in den meisten Ländern der Fall ist, kann die Wahrscheinlichkeit der Eineiigkeit gleichgeschlechtiger Zwillingspaare, die identische Blutgruppen haben, berechnet werden, ohne daß be-

sondere Zwillingsuntersuchungen vorher nötig sind. Blutgruppenbestimmungen können auch bei den Partnern eines Zwillingspaares unabhängig von Ort und Zeit gemacht werden.

Ein Vergleich der verschiedenen diagnostischen Methoden wurde versucht, um die Zahl und Art der Fehldiagnosen zu beleuchten.

Résumé

Il s'agit d'un travail qui est basé sur un matériel non sélectionné de jumeaux, collectionné et étudié il y a 20 ans par *Essen-Möller*. De ce matériel, *Essen-Möller* avait sorti un groupe de paires dont la monozygotie était prouvée par la présence d'une monochorie et un groupe de paires dizygotiques du même sexe, caractérisées par des groupes sanguins différents.

En réexaminant la simularité et dissimularité de ces paires de jumeaux, en se basant sur 15 traits anthropologiques, *Essen-Möller* a pu prouver la validité du test polysymptomatique pour les deux groupes et évaluer numériquement la valeur diagnostique de chacun des 15 traits.

En se servant d'autres groupes sanguins, les auteurs ont pu augmenter considérablement le groupe des paires dizygotiques en étendant ainsi la valeur des caractères anthropologiques pour le diagnostic des jumeaux bivitellins.

Ils ont constaté que spécialement l'iris, la couleur des cheveux et les empreintes digitales donnent des informations valables bien que la différence entre un jumeau et l'autre ne prouve pas la dizygotie contrairement aux groupes sanguins.

L'emploi de certains traits est limité à cause de la nécessité d'une comparaison des deux côtés. En outre, l'expression diagnostique numérique de la valeur diagnostique donnée dans ce travail ne peut pas être appliquée à d'autres populations avec une distribution différente des caractères en question.

Avec les groupes sanguins la preuve qu'il s'agit de jumeaux bivitellins du même sexe peut être obtenue dans plus de 95%, si on se sert de tous les groupes sanguins disponibles. Si la fréquence des gènes correspondants est connue, ce qui est le cas pour la plupart des pays, la probabilité d'une monozygotie chez des jumeaux du même sexe ayant les mêmes groupes sanguins peut être calculée sans que d'autres recherches spéciales soient faites préalablement. Les groupes sanguins ont l'avantage que les deux jumeaux peuvent être examinés séparément.

Les auteurs comparent finalement les différentes méthodes diagnostiques habituelles pour donner une estimation sur le nombre et le sens d'une fausse classification.

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A complete survey of the blood groups of the twins may be obtained from the authors.

Author's addresses: Dr. S. J. Dencker and Dr. L. Kaij, Psykiatriska Kliniken, *Lund* (Sweden). Dr. *M. Hauge* and Mr. Arne Nielsen, Universitetets Arvebiologiske Institut, 14 Tagensvej, *Copenhagen N* (Denmark)

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Genetics and Cancer. A Collection of Papers Presented at the Thirteenth Annual Symposium on Fundamental Cancer Research, 1959. University of Texas Press, Austin 1959. Pp. 459. $8.50.

A very fine group of scientists who have all contributed to the understanding of the processes underlying malignant growths have in this volume summed up a great number of experiments and facts concerning the relation between genetics and cancer. The introductory papers by *C. D. Darlington*, *Jack Schultz*, *Elie L. Wollman* and *François Jacob* discuss the genetic theory of cancer aetiology.

Analyses of nucleic acids of normal and malignant tissues and of tumour-inducing agents are reported, as well as the relation of radiation, genetic replication and chromosome status to carcinogenesis. The biochemical genetics of cultured cells is outlined. Gene action and interaction in experimentally produced and naturally occurring tumours, and the genetic basis of cell susceptibility and resistance are discussed. The chapter on heredity and human cancer is of special interest to human geneticists. *William J. Schull* surveys the developments of the last decade and suggests more intensive, especially biochemical, studies of the individuals in high risk families. *Newton E. Morton* deals with the methods of study in human genetics, a field to which he himself has made so many important contributions. *Madge T. Macklin* sums up the studies on human breast and gastric cancer, and finally *Clarence P. Oliver* comments on the genetic studies of families with high cancer incidence. An extensive subject index is included. *M. Hauge*, Copenhagen

Eldon J. Gardner: **Principles of Genetics.** John Wiley & Sons, Inc. New York 1960. Pp. VI + 366. $7.50.

This textbook is primarily written for students. It gives a full account of the basic principles of genetics with no special emphasis on human genetics, although many examples are taken from man. Extensive descriptions of many of the fundamental investigations and experiments leading to our present knowledge give the student a good introduction to the basic elements and ideas, and the study is further facilitated by instructive figures and schematic drawings. Only few and simple statistical principles are used and they are all fully explained. Among the other merits of the book it should be mentioned that the pioneers of genetics are not only named, but they are also portrayed by means of attractive drawings. *M. Hauge*, Copenhagen

G. Heuyer, M. Feld and J. Gruner (ed.): **Malformations congénitales du cerveau.** Masson et Cie, Paris 1959. Pp. 450, 231 figures. NF 50.00.

This volume contains a collection of papers on the aetiology, the morphogenesis and the pathological anatomy of the most important congenital malformations of the brain, especially anencephaly, hydrocephaly and the dysraphic syndroms. The chapter on aetiological problems clearly demonstrates our very limited knowledge and stresses the necessity of continued and extended studies in this area of teratology. The present work will be of great value in this research on account of its exhaustive descriptions of the fundamental processes and changes observed in these defects. Most of the papers are followed by bibliographies. No subject index is found. *M. Hauge*, Copenhagen

Bulletin der Schweiz. Ges. für Anthropologie und Ethnologie 1959/60. 36. Jahrgang. Büchler & Co. AG, Bern 1960. 75 Seiten, sFr. 11.–.

The „Bulletin der Schweizerischen Gesellschaft für Anthropologie und Ethnologie 1959/60" has appeared and brings some reports of anthropological studies, i.e. of blood groups and other normal traits in two populations in South India (Nilgiri and Kerala), and of variations of the skull measurements in the population of Valais, Switzerland. The bulletin may be obtained from the Redaktor, Gemeindestrasse 5, Zürich 7/32 (Switzerland).

Fuller, J. L. and Thompson, W. R.: **Behavior Genetics.** John Wiley & Sons Inc., New York 1960. X + 396 pages. $8.95.

This book offers a comprehensive account of current knowledge in this particular field of genetics. Since behavior is of interest to biologists as well as psychologists, the authors both of whom are experienced researchers prefer the term "behavior genetics" to "psychological genetics", which is reserved for psychometric studies.

It provides an introduction to the general principles and methods of genetics, a critical review of the literature from experimental and human studies, and, finally, the authors set forth their suggestions for further research. The list of references is extensive and most valuable.

The book should stimulate the rather sparse interest of genetics among clinical psychologists and psychiatrists, especially in the U.S.A. *N. Juel-Nielsen*, Risskov (Denmark)

L. S. Penrose: **Recent Advances in Human Genetics.** J. & A. Churchill Ltd, London 1961. Pp. 194. 27 sh. 6 d.

The book comprises eight reviews of subjects of current interest, chosen in fields where progress during later years has been substantial or pioneer work has been done.

Improved techniques of tissue culture in combination with new methods of preparation have paved the way for morphological studies of human chromosomes. The number of 46 has been finally established and several chromosomes have been morphologically characterized. Aneuploidy has been demonstrated in different clinical syndromes – *Turner*'s syndrome, *Klinefelter*'s syndrome, mongolism, a.o. The chromosome studies have deepened our understanding of sex determination and differentiation, and the sexual abnormalities are reviewed in new light.

Hand in hand with the morphological mapping of human chromosomes goes the elucidation of gene order by linkage studies. The absolute number of certain linkages is still small, but no doubt it'll rise quickly, partly because new marker loci are constantly added, partly because by refined biochemical and serological technique it is possible to disclose the heterozygotes in a growing number of recessive traits. In the timeconsuming calculations of these studies the electronic computer will be a useful tool.

The studies of normal and abnormal haemoglobins illustrate the approach to a biochemical mapping of the genetic material. For the first time in human genetics it is here possible to observe the primary effect of mutation on the amino acid sequence in the polypeptide chain.

The book is on the whole extremely well written and the list of authors comprises some eminent specialists in the different fields dealt with. The book satisfies a need for an accessible review of recent advances in the growing sphere of human genetics.

B. Harvald, Copenhagen

Stanley M. Garn: **Human Races.** C. C. Thomas, Springfield, Ill. 1961. 137 p., 26 ill. $ 5.50.

As a textbook in physical anthropology "Human Races" is rather different from previously existing works in this field. It is extremely condensed, although it includes a lot of new interesting findings. The author stresses very firmly that the study of human races is first of all a question of population genetics, and he seems to be refreshingly unaffected by previous systems of race classifications presented by various authors. The book is also free from the boring, endless descriptions which are so common in anthropological textbooks. Instead there is an emphasis on problems of causality and discussions of evolutionary processes.

Most of the recent findings concerning blood groups, serum groups and abnormal haemoglobins are reviewed in a clear and simple way. Each chapter includes a summary and a list of suggested readings.

The book can be recommended to the university student as a good, modern introduction to physical anthropology. *Lars Beckman*, Uppsala

J. Heremans: **Les globulines sériques du système gamma. Leur nature et leur pathologie.** Masson Paris 1960. Pp. 340. 72 fig. NF 69.–.

The immunoelectrophoretic method of serum protein analysis was introduced by *P. Grabar and C. A. Williams* in 1953. Dr. *J. Heremans*, one of the most experienced workers with this method, has compiled his results in a monograph with the above title.

After having described the modified technics used, the author gives an account of his investigations on the serum proteins of the beta-2 and gamma mobility. Of these, the beta-2 A globulin was isolated for the first time by Dr. *Heremans* (1957). The gamma globulin, the beta-2 A globulin and the beta-2 M globulin are grouped together to the so-called "*gamma system*" on the basis of carefully studied similarities in chemical, physical and immunological properties. In the following section, the *qualitative* abnormalities of the gamma system are elucidated. The *myeloma* proteins are classified into three types immunochemically: (A) Gamma type paraproteins (most common), (B) beta-2 A type paraproteins and (C) Bence-Jones type paraproteins (of low molecular weight). The findings in cases of *Waldenström*'s macroglobulinaemia and miscellaneous paraproteinaemias are reported.

The last section of the monograph treats the *quantitative* abnormalities of the gamma system in various diseases. In the chapter dealing with *antibody deficiency syndromes*, several points of interest for the geneticist are to be found. In most cases of congenital agammaglobulinaemia, all three components of the gamma system appear to be absent. However, Dr. *Heremans* describes some families with somewhat different protein abnormalities. One propositus had only traces of beta-2 A and gamma globulin, whereas the beta-2 M globulin was considerably increased; his clinically normal mother possessed no beta-2 A globulin. Another propositus lacked all three components, whereas his sister lacked only the beta-2 A. Finally, the complete absence of the beta-2 A globulin in a clinically normal adult male is mentioned. More detailed reports, in collaboration with Drs. *J. L. German and H. H. Fudenberg*, are foreseen with interest.

The monograph of Dr. *Heremans*, with its richness in facts and observations, ingeniously interpreted, clearly shows the important position immunoelectrophoresis has already occupied in the field of serum protein research. *Tore Leonhardt*, Malmö

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